3. REVIEW OF LITERATURE

3.1 CARDIOVASCULAR DISEASES (CVD)

Globally, cardiovascular diseases (CVD) constitute a leading cause of mortality. Developing countries like India are also struggling to manage the impact of CVD along with the growing burden of obesity, Type II diabetes and hyper-tension. Heart disease in India occurs 10 to 15 years earlier than in the West. One fifth of the deaths in India are from coronary heart disease (CHD). By the year 2020, it will account for one third of the deaths.

Current projections suggest that by the year 2020, India will have the largest CVD burden in the world. The prevalence of these diseases is more in urban than in rural areas. Lower vitamin C and selenium in Indians as compared to other ethnic groups, particularly in combination, could play a part in their increased risk of CHD. Lower vitamin C in Indians is probably because of its destruction by prolonged cooking. There are epidemiological correlations between poor plasma levels of essential antioxidants and the risk of coronary heart disease.

Epidemiological studies have revealed many important risk factors of environmental and genetic origin that are associated with atherosclerosis. The most important clinical complication is an acute occlusion due to blood clot formation during rupture of the lesion, resulting in myocardial infarction. One of the major initiating event in atherosclerosis is oxidative damage to the cholesterol component of the LDL known as LDL oxidation. An appropriate balance between processes that stimulate or inhibit oxidative stress, LDL oxidation, and additional LDL atherogenic modifications determines the progression of atherogenesis.
LDL oxidation and atherogenesis can be inhibited by antioxidants. Elevation in the activity of nutritional antioxidants over the damaging effects of pro oxidants has the potential to attenuate atherosclerosis, which is a leading cause of mortality in several human populations. There are also epidemiological evidences and interventional studies to correlate higher level of antioxidant-rich food uptake with lower incidence of CHD. The prevalence of CHD increased from 1% to over 8% in urban population. Indians have among the highest prevalence of CHD and have rather unusual risk factors characterized by high triglycerides, low High Density Lipoproteins (HDL), glucose intolerance, insulin resistance, abdominal obesity and increased lipoprotein (a) levels. Hence there is an urgent need to explore various strategies to combat the increasing risk of CVDs in the Indian subcontinent. Medicinal plants with cardioprotective effects can play a major role in this aspect.

**Oxidative Stress, Antioxidants and CVD**

Evidence for the involvement of free radicals in the etiology of CHD comes from several studies that suggest a correlation between antioxidant intake and various CVDs. Antioxidant defenses also appear to be a distinguishing factor between normal subjects and those with symptomatic CHD. Antioxidants remain higher in normal subjects and keep lipid peroxidation (LP) under control. In symptomatic CHD, antioxidant levels are significantly lowered. Hence, increased intake of antioxidants, especially lipid-soluble and chain-breaking antioxidants that accumulate in lipoproteins, might be expected to have beneficial effects. A large number of studies in experimental animals have shown that hypercholesterolemia, diabetes, hypertension, smoking, ageing and nitrate intolerance are the common risk factors for atherosclerosis. They increase production of free radicals not only by endothelial cells but also by vascular smooth muscle cells and adventitial cells. However, the
defense system in terms of exogenous antioxidants, i.e. natural compounds such as curcumin, baicalein and resveratrol prevent atherosclerosis formation by exhibiting radical scavenging effects\textsuperscript{37}, as shown in Figure-
Medicinal Plants with Cardioprotective Properties

In recent times, there is a lot of interest in ‘phytonutrients’ from plants with potential benefits. While these phytonutrients are not essential by traditional definitions, they apparently reduce risks of diseases. A large number of epidemiological studies show that diets rich in fruits and vegetables, i.e. foods rich in antioxidants, are associated with lower incidence of CVDs. Apart from these dietary sources, Indian medicinal plants are also known for their cardioprotective properties and are rich sources of antioxidants. Many plants have been used for cardioprotection in the traditional Indian medicinal system. A review of such plants with cardioprotective/ antioxidant effects was carried out. Several herbs and herbal products have been recommended to promote a healthy heart. These include garlic, guggulipid, tocotrienols derived from palm oil, soy protein isoflavones, and Chinese red yeast rice. They have been shown to lower cholesterol levels by different mechanisms. Other antioxidant-rich and antiangiogenic herbs such as green tea, black tea, and red wine have the potential to reduce the progression of atherosclerosis\textsuperscript{38}. 
Table 3.1

<table>
<thead>
<tr>
<th>Indian medicinal plants</th>
<th>Antioxidant effects</th>
<th>Cardioprotective effects</th>
<th>Other therapeutic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Allium sativum</em> (garlic)</td>
<td>Oils isolated from garlic inhibit nicotine-induced lipid peroxidation in rat tissues; Aqueous garlic extract (250 mg/kg) decreases lipid peroxidation, increases GPX, GST and GSH during buccal pouch carcinogenesis in Syrian male hamsters</td>
<td>Cardioprotective, hypolipidaemic, antithrombotic, mild cholesterol lowering effect and reduces blood clotting</td>
<td>Antimicrobial, antiarthritic; antitumor, hypoglycemichepatoprotective and anticarcinogenic</td>
</tr>
<tr>
<td><em>Allium cepa</em> (onion)</td>
<td>Oils isolated from onion inhibit nicotine-induced lipid peroxidation in rat tissues</td>
<td>Cardioprotective, hypolipidaemic, antithrombotic</td>
<td>Antimicrobial, antitumor, hypoglycemic, antiarthritic</td>
</tr>
<tr>
<td><strong>Asparagus racemosus</strong> (shatavari)</td>
<td>Purified polysaccharide fraction inhibited (\gamma)-radiation-induced lipid peroxidation in rat liver mitochondria</td>
<td>Ayurvedic preparation using this, abana, gives cardioprotection</td>
<td>Immunomodulator, anti-stress agent, antihepatotoxic</td>
</tr>
<tr>
<td><strong>Caesalpinia bonducella</strong></td>
<td>Leaves decreased lipid peroxidation and increased GSH, SOD, and CA</td>
<td>Decreases blood glucose levels significantly</td>
<td>Anti-diabetic, antipyretic, analgesic, antitumor.</td>
</tr>
<tr>
<td><strong>Cassia fistula</strong></td>
<td>Aqueous extract of flowers decreased levels of CD, LOOH, TBARS and restored GSH, SOD, CAT, GPX, GR in diabetic rat heart tissues</td>
<td>Used for treatment of cardiovascular diseases</td>
<td>Hepatoprotective, antidiabetic, antitumor</td>
</tr>
<tr>
<td><strong>Curcuma longa</strong> (turmeric)</td>
<td>Natural curcuminoids act as antioxidants; turmeric extracts have</td>
<td>Decreases proliferation of smooth muscles in blood vessels, protects from blockage of arteries</td>
<td>Anticarcinogenic, anti-inflammatory, radioprotective, hepatoprotective and anticlastogenic</td>
</tr>
</tbody>
</table>
antioxidant effects, curcumin inhibits 1O2-induced DNA damage

<table>
<thead>
<tr>
<th><strong>Emblica officinalis</strong> (Amla)</th>
<th>Inhibits TBARS formation and increases SOD, CAT, GPX during oxidative stress in rat brain</th>
<th>Hypolipidemic, decreases ischemia-reperfusion-induced oxidative stress in rat heart</th>
<th>Anti-inflammatory, hepatoprotective, anticandidal, cytoprotective, anticlastogenic, anti-ulcer, anti-pyretic, anti-tumor and analgesic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Garcinia indica</strong> (kokum)</td>
<td>Garcinol is a good antioxidant and inhibits iNOS induction in astrocytic cells</td>
<td>Cardiotonic</td>
<td>Neuroprotective, anti-inflammatory, anti-tumor.</td>
</tr>
<tr>
<td><strong>Hemidesmus indicus</strong> (anantmul)</td>
<td>Inhibition of free radical formation, inhibits LP, increases SOD</td>
<td>Caps HT2, a herbal Ayurvedic medicine is antiatherogenic</td>
<td>Anti snake venom activity, anti-pyretic, anti-inflammatory, antipyretic</td>
</tr>
<tr>
<td><strong>Ocimum sanctum</strong> (tulsi)</td>
<td>Orientin and vicenin inhibited radiation induced lipid peroxidation in vivo; Ocimum seed oil</td>
<td>Hypoglycaemic in diabetic rats, cardiac protection in isoproterenol induced myocardial infarction in rats.</td>
<td>Chemoprotectant, anti-thyroid, radioprotective, neuroprotective, anti-ulcerogenic</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Properties</td>
<td>Effects</td>
<td>Benefits</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><em>Phyllanthus amarus</em></td>
<td>Antioxidant, increases SOD, GST, GPX</td>
<td>Significantly reduces blood glucose</td>
<td>Anti-diabetic, antiinflammatory, anti-mutagenic, antidiarrhoeal Radioprotective</td>
</tr>
<tr>
<td><em>Picrorrhiza kurroa</em> (katuka)</td>
<td>Alcoholic extract prevented lipid peroxidation and increases activities of SOD, CAT during D-galactosamine induced hepatitis in rats</td>
<td>Cardioprotection against isoproterenol-induced myocardial stress in rats, hypolipidaemic</td>
<td>Hepatoprotective, anti-allergic, antidiabetic, anti-ulcerogenic, antileishmanial</td>
</tr>
<tr>
<td><em>Terminalia arjuna</em> (arjun)</td>
<td>Potent free radical scavenger, inhibits oxidative damage to lipids, proteins and DNA in rats</td>
<td>Cardiotonic, cardioprotective, hypocholesterolaemic, anti-anginal, anti-ischemic, hypolipidemic, anti atherosclerotic</td>
<td>Hepatoprotective, antimitagenic, anticarcinogenic, anti-haemorrhagic, induces union of fractures</td>
</tr>
<tr>
<td>Plant</td>
<td>Activity</td>
<td>Benefits</td>
<td></td>
</tr>
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<td>---------------</td>
<td>-----------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><em>Trigonella foenum-graecum</em> (fenugreek)</td>
<td>Antioxidant in diabetic rats</td>
<td>Decreased blood glucose levels, lowers cholesterol, LDL, VLDL, triglycerides</td>
<td>Antidiabetic activity</td>
</tr>
<tr>
<td>Vitis vinifera (grapes)</td>
<td>Antioxidant activity due to isoflavons</td>
<td>Cardioprotective</td>
<td>Antiinflammatory, chemopre-ventive; antimutagenic</td>
</tr>
<tr>
<td>Withania somnifera (ashwagandha)</td>
<td>Sitoinosides VII-X and withaferin A increased SOD, CAT, GPX in rat frontal cortex and striatum</td>
<td>Cardioprotective and anticoagulant</td>
<td>Immunomodulatory, anti-inflammatory, anti-aging, anti-stressor, anticarcinogenic and thyroidstimulatory</td>
</tr>
<tr>
<td>Zingiber officinalis (ginger)</td>
<td>Lowers lipid peroxidation and maintains SOD, CAT, GPX and increased blood GSH levels in rats</td>
<td>Cardiotonic</td>
<td>Carminative, antibacterial, phrodisiac, general tonic, blood purifier, antiinflammatory</td>
</tr>
</tbody>
</table>
3.2 MYOCARDIAL INFARCTION

Cardiovascular Diseases (CVD) remain one of the principle causes of mortality despite several advancements in the medical interventions. Among these complications the ischemic heart diseases, acute myocardial infarction (AMI) in particular, is one of the most alarming values. Acute myocardial infarction, which arises out of a lot risk-factors working in concert, gives rise to a lot of unfavorable biochemical and enzymatic outcomes. It is the acute condition of myocardial necrosis that occurs as a result of imbalance between coronary blood supply and myocardial demand. The patient may experience significant disability or die. Experimental and clinical studies have exhibited that there is increased generation of ROS such as superoxide anion (UO$_2^-$) and hydroxyl radicals (UOH) in heart failure, which involved in the formation of lipid peroxides, damage of cell membrane, and destruction of antioxidative defense system. Therapeutic intervention via suppression of free radical generation and/or enhancement of endogenous antioxidant enzymes may limit the infarct size and attenuate myocardial dysfunction.

At last of which is the ultimate morbidity or even death. The synthetic drugs that constitute the current pharmacological armamentarium are themselves effective in managing the condition but not without side effects. Therefore, accelerated the need for natural medicine, which may be use as dietary supplement to prevent the development of AMI.
Necrosis begins in a small zone of the myocardium beneath the endocardial surface in the center of the ischemic zone. This entire region of myocardium (shaded) depends on the occluded vessel for perfusion and is the area at risk. Note that a very narrow zone of myocardium immediately beneath the endocardium is spared from necrosis because it can be oxygenated by diffusion from the ventricle. The end result of the obstruction to blood flow is necrosis of the muscle that was dependent on perfusion from the coronary artery obstructed. Nearly the entire area at risk loses viability. The process is called myocardial infarction, and the region of necrotic muscle is a myocardial infarct.

Myocardial infarction is ischaemic necrosis of a part of the myocardium due to sudden occlusion of a branch of coronary artery of heart. A sudden and acute
thrombus at the site of atherosclerotic obstruction is the usual cause. About 25% patients die before treatment can be instituted. The remaining patients are treated in specialized coronary care units with continuous monitoring of the hemodynamic parameters and selection of drugs and dosage based on ECC. Those patients receive such immediate facility fast benefitted by drug therapy, which according to individual patients needs is directed situations:

- **Pain, anxiety and apprehension** - Opioid analgesics (morphine/pethidine), diazepam adminstered parenterally
- **Oxygenation** - By O₂ inhalation and assisted respiration, if needed.
- **Maintenance of blood volume, tissue perfusion and microcirculation** - Slow i.v. infusion of saline/low molecular weight dextran (avoid volume overload).
- **Correction of acidosis** - Due to lactic acid production-sod. bicarbonate by i.v. infusion.
- **Prevention and treatment of arrhythmias** - Prophylactic i.v. infusion of a β blocker (unless contraindicated) as soon as the MI patient is seen and its continuation orally for a few days has been shown to reduce the incidence of arrhythmias and mortality. β-blockers used early in evolving MI can reduce the infarct size (myocardial salvage) and subsequent complications. Tachyarrhythmias may be treated with lidocaine, procainamide or other antiarrhythmics. Routine prophylactic lidocaine infusion is not recommended now. Bradycardia and heart block may be managed with atropine or electrical pacing.
- **Pump failure** - The objective is to increase c.o. and / or decrease filling pressure without unduly increasing cardiac work or reducing BP. Drugs
used for this purpose are: (a) Furosemide (b) Vasodilatols (c) Inotropic agents

- **Prevention of thrombus extension, embolism, venous thrombosis** - Aspirin (162-325 mg) should be given for chewing and swallowing as soon as MI is suspected (if not already being taken on a regular basis). This is continued at 80-160 mg/day. Anticoagulants (heparin followed by oral anticoagulants) are used primarily to prevent deep vein thrombosis.

- **Thrombolysis** - Fibrinolytic agents, i.e. plasminogen activators-streptokinase/urokinase/alteplase to achieve reperfusion of the infarcted area.

- **Prevention of remodeling and subsequent CHF** - ACE inhibitors/ARBs are of proven efficacy and afford long-term survival benefit.

- **Prevention of future attacks** - (a) Platelet inhibitors-aspirin or given on long-term basis are routinely prescribed. (b) B blockers-reduce risk of reinfarction, CHF and mortality. All patients not having any contraindication are put on a β-blocker for at least 2 years. (c) Control of hyperlipidaemia-dietary substitution with unsaturated fats, hypolipidemic drugs.

### 3.2.1. Isoproterenol Induced Myocardial Infarction

The isoproterenol-induced MI in rats offers a relevant model to study the effect of natural products. The method is simple in execution and the biochemical, histological and electrocardiographic wave alteration seen in case of an acute myocardial infarction. This model has been widely used by many researchers to study the effect of drugs in AMI.
Recent attention has been focus on non nutrient phytochemical such as flavonoids and alkaloids and xanthone derived from different plants species as potential therapeutic compounds in prevention and management of CVD due to presence of antioxidants. Phytochemical or natural products like crude extracts, herbals, herbal mineral formulations and polyherbal formulations have been used for the treatment and prevention of ischemic heart diseases in traditional systems of medicine. A variety of herbal products have been tried for activity against acute myocardial infarction with considerable success.

Catecholamines at minimum amount are considered to be beneficial in monitoring or regulating heart function by exerting a positive inotropic effect. Catecholamines administration at high amount or excess release of it from the endogenous stores may deplete the energy reserve of cardiomyocytes and thus may result in biochemical and structural changes in heart which are responsible for the development of irreversible damage of myocardial tissue. Isoproterenol [L-β-(3, 4-dihydroxyphenyl)-α-isopropylaminoethanol hydrochloride] is a sympathomimetic beta adrenergic receptor agonist, causes severe stress to the myocardium resulting in an infarct like necrosis of heart muscle. The rat model of isoproterenol-(ISO) induced myocardial necrosis serves as a well accepted standardized model to evaluate several cardiac dysfunctions and to study the efficacy of various natural and synthetic cardioprotective agents. Isoproterenol induced myocardial infarction is commonly used experimental model for several reasons due to an excellent reproducibility, extraordinary technical simplicity, as well as an acceptable low mortality.
Myocardial infarction induced by isoproterenol has been reported to exhibit various metabolic and morphologic changes in the heart tissue of the experimental animals similar to those observed in human myocardial infarction. Isoproterenol induced necrosis is maximal in the sub endocardial region of the in the interventricular septum and left ventricle \(^{43,44}\).

### 3.2.2 Mechanisms of Isoproterenol induced myocardial infarction:

Several molecular mechanisms for the cardiotoxic effects of high levels of Isoproterenol have been suggested. These mechanisms are:

- (A) Functional hypoxia and ischemia
- (B) Coronary insufficiency
- (C) Alterations in metabolism
- (D) Decreased level of high-energy phosphate stores
- (E) Intracellular \(Ca^{2+}\) overload
- (F) Changes in electrolyte contents and
- (G) Oxidative stress

Although these changes show individual pathological conditions, they affect each other and thus are interpreted as complex entities to induction of diabetic neuropathy.

Oxidative stress, which due to free radicals species are most probably, one of the main mechanisms through which catecholamines (symathomimetic) exert their toxic effects. Spontaneously, oxidation of catecholamines results in the formation of catecholamine-o-quinones, which produce aminochromes through cyclization. Adrenochrome (which results from the cyclization of epinephrine-o-quinone) could be oxidized to various other compounds such as adrenolutin, 5, 6-dihydroxy- 1-
methylindole (DHMI) or adrenochrome-adrenolutin dimer. All these reduction-oxygen reactions generate free radicals. Consequently, catecholamine-o-quinones, aminochromes and free radical species (ROS) resulting from the oxidation of catecholamines are thought to be involved in catecholamine-related toxicity.

The oxidized products (ROS) have the ability to interact with sulphydryl groups of various proteins or enzymes and also promotes to production of superoxide anions and subsequently hydrogen peroxide. These results in alteration in microsomal permeability, mitochondrial calcium uptake, decrease in ATP production and the formation of highly reactive hydroxyl radicals (OH\(^{-}\)) which causes protein, lipid and DNA destruction. Isoproterenol alter a number of biochemical and electrophysiological functions. These also responsible for change the histological architecture in the heart.

The basic disturbances of isoproterenol induced myocardial infarction have been indicated to enhance adenyl cyclase activity which is resulting in increased cAMP formation and turn would lead to the higher lipid accumulation in the myocardium. Number of early events, such as ultrastructural changes, histological changes, biochemical alteration, electrolyte and membrane changes, has been exhibited to occur within 48 hours after the injection (subcutenously) of isoproterenol. Fat deposition and glycogen depletion and have been reported. Myocardial histological architecture changes induced by excessive amounts of isoproterenol include degeneration and necrosis of myocardial fibres, accumulation of inflammatory cells, interstitial edema, lipid droplets and endocardial hemorrhage.

Biochemical alterations in ISO-induced cardiomyopathy represent a complex pattern of changes in cardiac marker enzymes, lipid profile, lipid metabolizing enzymes, enzymatic and non-enzymatic antioxidants levels, glycoproteins levels,
decrease in ATP store and changes in electrolyte levels in the blood as well as in the myocardial tissue. Changes including those in sarcolemma, sarcoplasmic reticulum and mitochondria, are mainly mediated by oxidative stress, which is known to result in alterations of enzyme activity and transport systems and cause disturbances in cellular homeostasis. One of the important determinants of ISO induced myocardial injury is Lipolysis. Study also reported evidence that chronic β-AR (beta adrenergic receptors) stimulation markedly exhibited iNOS up-regulation, CRP release and nitrative stress and that iNOS-mediated nitrative stress functions as a main interface linking chronic β-AR activation and myocardial cell necrosis.45,46,47

3.2.3 Protective Role of Natural Products In Myocardial Infarction

A promising Approach For Natural Products:

Herbal products are increasing gaining greater acceptance from the public and medical profession due to advances in the understanding of the mechanisms by which these herbs positively affects health and quality of life of human beings. Better understanding of mechanism of action is the discovery of herbs as highly antioxidants and potent free radical scavenger. Natural antioxidants, especially flavonoids and phenolics are safe and effective. Therefore, in current time, substantial focus has been directed towards credentials of plants with antioxidant ability and free radical scavenger activity that may be benefits for human expenditure. Many disease conditions has been well customize due to free radicals. Number of biochemical reactions in our body generates reactive oxygen species and these are capable of damaging critical bio-molecules. In recent years one of the areas which attracted a great focus on antioxidant in the control of degenerative diseases in which oxidative stress has been implicated.48
In recent years, substantial interest has been attention on antioxidant therapeutic strategies for cardiovascular disease (CVD). That one is imperative to emphasize effective prevention strategies for the cardiovascular complications. In past decades, fruit, vegetable and antioxidant rich mediterranean diets have been highlighted, because of a number of epidemiological studies have provided a strong inverse relationship between cardiovascular disease and fruit rich and vegetable diets. The WHO recommends 500 g of fresh fruits and vegetables daily. Antioxidant micronutrients have focused, particularly vitamin C, vitamin E, β-carotene and other carotenoids, such as zeaxanthin, lutin, and lycopene, which have the greatest singlet oxygen-quenching activity.

**Polyherbal and herbomineral formulations:**

Several scientific reports have proved that polyherbal and herbomineral formulations are also useful and benefits in the prevention of isoproterenol induced myocardial infarction in rats. Arogh a polyherbal formulation is a cocktail of nine herbs including *Nelumbo nucifera*, *Rosa damasana*, *Hibiscus rosasinensis*, *Hemidesmus indicus*, *Querus infectoria*, *Terminalia chebula*, *Zingeber officinalis*, *Eclipta alba*, and *Glycrrhiza glabra*. Arogh treatment in isoproterenol induced myocardial infarction showed significant alteration in the activities of endogenous antioxidant enzymes and certain biochemical parameters. For example, DHC-1 is a herbal formulation derived from the popular plants *Emblica officinalis*, *Syzygium aromaticum*, *Glycyrrhiza glabra*, *Bacopa monniera* and *Mangifera indica* was studied for its antioxidant property. Serum markers significantly reduce of heart and the extent result of lipid peroxidation with a concomitant increase in the enzymatic (SOD and CAT) and non-enzymatic antioxidants (reduced glutathione) were observed in DHC-1 pretreated animals compared with the isoproterenol treated animals (control
Another example is Marutham, a polyherbal formulation on serum and heart tissue lipids, serum lipoproteins and heart membrane bound enzymes in isoproterenol induced myocardial infarction was reported in wistar rats. Pretreatment with Marutham at different doses of 30, 60 and 90 mg kg\(^{-1}\) to isoproterenol treated rats significantly prevented the altered lipid profile and membrane bound enzymes to near normal group status. A herbomineral formulation containing extract obtained from *speciosa*, *Ceutella asiatica*, *Tribulus terrestris*, *Asparagus racemosus*, *Piper lengum*, *Anacyclus pyrethrus*, *Nux vomica* and *Tinospora cordifolia* *Mucuna pruriens*, *Withania sominera*, *Shring bhasma* and *Argyreia* was studied in isoproterenol model of myocardial infarction in rats. It was observed this herbal formulation reduced the serum levels of creatine, urea, blood urea nitrogen (BUN) and uric acid. It was further found that administration of this formulation increased the level of superoxide dismutase, catalase, reduced glutathione and membrane bound enzymes and decreased significantly the level of lipid peroxidation in heart. Similarly, Abana, a polyherbal formulation containing a mixture of *Terminalia chebula*, *Phyllanthus emblica*, *Nardostachys*, *jatamansi*, *Tinospora cordifolia*, *Glycyrrhiza glabra*, *Zingiber officinale*, *Nepeta hindostanawas Terminalia arjuna* and *Withania sominera*, evaluated for activity against isoproterenol induced myocardial infarction in albino rats. They have attributed the positive effect to various compounds present in the formulation, which have previously reported antioxidant activity\(^{51,52}\).
3.3 CARDIAC ARRHYTHMIA

An arrhythmia may occur as a result of heart disease or from a disorder that affects cardiovascular function. Conditions such as emotional stress, hypoxia, and electrolyte imbalance also may trigger an arrhythmia. An electrocardiogram (ECG) provides a record of the electrical activity of the heart. The heart beats regularly during normal rhythm which generates a single coordinated electrical wave that is recorded as a normal electrocardiogram (ECG). In arrhythmic conditions such as ventricular tachycardia and ventricular fibrillation, normal behavior is disrupted and the ECG is recorded at rapid rates with increased complexity.

Arrhythmias are disorders of heart rhythm. They are due to abnormalities in impulse generation, impulse conduction, or a combination of both. Abnormalities of impulse generation include abnormalities of automaticity and early or delayed after depolarization with triggered activity. Abnormalities of impulse propagation include conduction block and re-entry of the cardiac impulse.

The basic reason of many arrhythmias is the development of a repetitive circuit of electrical activity which stimulates the heart continuously and produces contractions at a rapid rate. During tachycardia, a single wave can be rotated as a spiral wave which is producing fast rates and complexity. During fibrillation, a single spiral wave can be degenerated into multiple waves. Due to arrhythmia, the heart’s ability to pump blood sometimes may be lethal. Combination of abnormalities of impulse formation and propagation can produce complex arrhythmias.

In any arrhythmia, it is useful to know which cardiac tissue participates, the ionic mechanisms and structural abnormalities that promote it. Supraventricular and ventricular arrhythmias differ in origin, ECG changes and clinical manifestations, based on which one must be able to distinguish between supraventricular from
ventricular arrhythmias. The mechanism underlying clinical cardiac arrhythmias are of considerable significance and it is unfortunate that these arrhythmias are not easily studied in clinical situations.\textsuperscript{53,54}

**IMPORTANT MECHANISMS OF CARDIAC ARRHYTHMIA\textsuperscript{55}**

**A. Enhanced/ectopic pacemaker activity**

The slow phase-4 depolarization may be increased pathologically in the automatic fibres or such activity may appear in ordinary fibres resulting in sinus tachycardia, atrial and ventricular extrasystols (ES) or tachycardias, atrial flutters (AF). Actopic pacemaker activity may result from current of injury. Myocardial cells damaged by ischaemia become partially depolarized: a current may flow between these and normally polarized fibres (injury current) and initiate an impulse.

**B. After-depolarizations**

These are secondary depolarizations accompanying a normal or premature action potential

**Early after-depolarization (EAD)**

Repolarization during phase-3 is interrupted and membrane potential oscillates. If the amplitude of oscillations is sufficiently large, neighbouring tissue is activated and a series of impulses are propagated. EADs are frequently associated with long Q-T interval due to slow repolarization and prolonged APs. They result from depression of delayed rectifier $K^+$ current

**Delayed afterdepolarization (DAD)**

After attaining resting membrane potential (RMP) a secondary deflection occurs which may reach threshold potential and initiate a single premature AP. Generally result from Ca\textsuperscript{2+} overload (digitalis toxicity, ischaemia-reperfusion). Because an AP is
needed to trigger after-depolarizations, arrhythmias based on these have been called triggered arrhythmias.

C. Reentry

Due primarily to abnormality of conduction, an impulse may recirculate in the heart and cause repetitive activation without the need for any new impulse to be generated. These are called reentrant arrhythmias.

(i) Circus movement type

It occurs in an anatomically defined circuit. A premature impulse, temporarily blocked in one direction by refractory tissue, makes a one-way transit around an obstacle (natural orifices in heart, infarcted or refractory myocardium), finds the original spot in an advanced state of recovery and reexcites it, setting up recuffent activation of adjacent myocardium (Fig. 3.4). Reentry occurring in an anatomically fixed circuit can be permanently cured by high radiofrequency catheter ablation of the defined pathway.

![Diagram of circus movement reentry in atrium](image)

Fig.3.3 Diagrammatic depiction of circus movement reentry in atrium

(ii) Microreentry circuit

It may form at the junction of a Purkinje fibre (PF) with ordinary ventricular fibre (gate region). One of the branches of the PF may get sufficiently depolarized to cause unidirectional block (Fig 3.5). Extremely slow conduction at this site due to slow
channel depolarization and markedly abbreviated action potential duration (APD) and effective refractory period (ERP) makes reentry possible in a short loop of tissue. For reentry to occur, the path length of the circuit should be greater than the wave length (ERP x conduction velocity) of the impulse. Slow conduction in the reentrant circuit may be caused by:

(a) Partial depolarization of the membrane-decreased slope of phase 0 depolarization, i.e. depressed fast channel response.

(b) Cells changing over from fast channel to slow channel depolarization which conducts extremely slowly. When a fibre is depolarized to a RMP of about -60 mv, the Na\(^+\) (fast) channels are inactivated, but it can still develop Ca\(^{2+}\) (slow) channel response.

![Diagrammatic depiction of microreentry circuit in ventricle](image)

**Fig. 3.4** Diagrammatic depiction of microreentry circuit in ventricle

**D. Fractionation of impulse**

When atrial ERP is brief and inhomogeneous (under vagal overactivity), an impulse generated early in diastole gets conducted irregularly over the atrium, i.e. it moves rapidly through fibres with short ERP (which have completely recovered) slowly through fibres with longer ERP (partially recovered) and not at all through those still refractory. Thus, Asynchronous activation of atrial fibres occurs - atrial fibrillation (AF). This arrhythmia must be initiated by a premature depolarization but is self
sustaining, because passage of an irregular impulse leaves a more irregular refractory trace and perpetuates the inhomogeneity of ERPs.

Table 3.2 The important cardiac arrhythmias are:

<table>
<thead>
<tr>
<th>ARRHYTHMIA</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial flutter</td>
<td>Rapid contraction of the atria (up to 300 bpm) at a rate too rapid for the ventricles to pump efficiently</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Irregular and rapid atrial contraction, resulting in a quivering of the atria and causing an irregular and inefficient ventricular contraction</td>
</tr>
<tr>
<td>Premature ventricular contractions</td>
<td>Beats originating in the ventricles instead of the sinoatrial node in the atria, causing the ventricles to contract before the atria and resulting in a decrease in the amount of blood pumped to the body</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>A rapid heartbeat with a rate of more than 100 bpm, usually originating in the ventricles</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>Rapid disorganized contractions of the ventricles resulting in the inability of the heart to pump any blood to the body, which will result in death unless treated immediately</td>
</tr>
</tbody>
</table>

Normal QRS complex
Fig. 3.5 Abnormal rhythms due to defects in impulse formation.
Table 3.3
Antidysrhythmic drugs unclassified in the Vaughan Williams' system\textsuperscript{56}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>Sinus bradycardia</td>
</tr>
<tr>
<td>Adrenaline (epinephrine)</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>Heart block</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Rapid atrial fibrillation</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>Ventricular tachycardia due to hyperkalaemia</td>
</tr>
<tr>
<td>Magnesium chloride</td>
<td>Ventricular fibrillation, digoxin toxicity</td>
</tr>
</tbody>
</table>

Class

I. Membrane stabilization agents
   (Na\textsuperscript{+} Channel blockers)
   A. Moderately decrease dv/dt of 0 phase- Quinidine, Procainamide, Disopyramide, Moricizine
   B. Little decrease in dv/dt of 0 phase- Lidoceaine, Mexiletine
   C. Markedly decrease in dv/dt of 0 phase- Propafenone, flecainide

II. Antiadrenargic agents (β-blockers)- Propranolol, Esmolol, Sotelol (also class III)

III. Agents widening AP (prolong repolarization and ERP)- Amiodarone, Bretylium (also class II), Dofetilide

IV. Calcium channel blockers- Varpamile, Diltiazem

Now a days, sophisticated electro-physiological techniques are available to study cardiac pathophysiology, both in vivo and in vitro. These techniques have
enabled to study the underlying mechanisms of arrhythmias and conduction disturbances in both experimental models and in patients. Although our knowledge of the mechanisms of arrhythmias and conduction disturbances has greatly increased, much remains to be explored.

Various animal models [Table 3.4] have been developed for supraventricular as well as ventricular tachycardia to understand the basic cause, origin, possible mechanisms, manifestations and for development of new therapeutic strategies. Supraventricular tachycardia in an animal model closely resembles the clinical features observed in the patients. But ventricular models are fraught with problems since they cannot be studied in human patients because of the unpredictable occurrence in situations, where electrophysiological changes may develop within minutes. Besides this, many other factors determine whether, and if so how of ventricular arrhythmias occur in the setting of acute ischaemia and/or a chronic myocardial infarction. In experimental models, usually only a single factor is taken into account. Though, an animal is not the same as a human patient, arrhythmogenic mechanisms derived from animal experiments have tremendously helped us to diagnose and adapt therapeutic strategies.$^{57}$
### Table 3.4

**Animal models to induce cardiac arrhythmias**

<table>
<thead>
<tr>
<th>Type of arrhythmia</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraventricular tachycardia Wolf-</td>
<td>Pre-excitation in dogs</td>
</tr>
<tr>
<td>Parkinson-White syndrome</td>
<td>Transgenic mice (PRKAG2 over expression</td>
</tr>
<tr>
<td>Re-entrant arrhythmia of AV node</td>
<td>Isolated rabbit heart preparation</td>
</tr>
<tr>
<td></td>
<td>Isolated rabbit heart atrium preparation, including the AV node and</td>
</tr>
<tr>
<td></td>
<td>the AV node and Bundle of His</td>
</tr>
<tr>
<td></td>
<td>Blocked of atrial impulses from the anterior input site to the</td>
</tr>
<tr>
<td></td>
<td>AV node in dogs</td>
</tr>
<tr>
<td></td>
<td>Isolated canine AV nodal preparation</td>
</tr>
<tr>
<td>Atrial Flutter</td>
<td>Canine right atrial crush injury model</td>
</tr>
<tr>
<td></td>
<td>Atrial flutter induced by acetylcholine (ACh) and rapid pacing in</td>
</tr>
<tr>
<td></td>
<td>the dog</td>
</tr>
<tr>
<td></td>
<td>Atrial flutter by aconitine</td>
</tr>
<tr>
<td></td>
<td>Right atrial enlargement model of atrial flutter</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>Atrial fibrillation by atrial ischaemia in dogs</td>
</tr>
</tbody>
</table>
|                                        | PACAP-27 induced biphasic chronotropic effect and atrial fibrillation.
|                                        | Atrial fibrillation in dogs by atrial burst pacing                  |
|                                        | Canine model of chronic atrial fibrillation                         |
|                                        | Vagal atrial fibrillation                                           |
|                                        | Atrial Fibrillation in the isolated Langendorff-perfused rabbit     |
|                                        | heart                                                               |
|                                        | Atrial Fibrillation by fibrillation pacemaker                       |
|                                        | Atrial fibrillation by aconitine                                    |
### 3.4 THE PATHOLOGY AND TREATMENT OF CARDIAC ARRHYTHMIAS: FOCUS ON ATRIAL FIBRILLATION

Atrial fibrillation (AF) is a kind of sustained cardiac arrhythmia. The arrhythmia has a prevalence of 1% and is age dependent with ~15% of patients. The increasing epidemiological significance of Atrial fibrillation is further projected statistically which predicts that AF prevalence may have increased up to 2.5-fold by the year 2050. In senile patients the development of AF is generally related to cardiac abnormality, whereas younger patients may develop AF in the absence of underlying heart disease (“lone AF”).

Most common symptoms of AF are rapid and irregular heartbeat palpitations, dizziness, lightheadedness, anxiety, and reduced exercise capacity. However, one third of patients show no symptoms and unaware of abnormal heart rhythm, preventing early detection and timely introduction of therapies. In case of chronic patients the arrhythmia may be triggered by cardiac or thoracic surgery, infections, alcohol intake, excessive nicotine or caffeine consumption, hypoglycemia, electrolyte

<table>
<thead>
<tr>
<th>Ventricular fibrillation</th>
<th>Porcine model of VF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ventricular fibrillation induction by 60-hz alternating current in isolated swine right ventricle</td>
</tr>
<tr>
<td></td>
<td>Ventricular arrhythmia by various chemicals</td>
</tr>
<tr>
<td></td>
<td>Ischaemia induced ventricular arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Ventricular arrhythmia during exercise by ischaemia</td>
</tr>
<tr>
<td></td>
<td>Stretch induced arrhythmias in isolated canine ventricle</td>
</tr>
<tr>
<td></td>
<td>Model for sudden cardiac death</td>
</tr>
<tr>
<td></td>
<td>Canine model of two stage ligation</td>
</tr>
</tbody>
</table>
imbalances, and physical or emotional stress. Based on these data, interventional and pharmacological therapies targeting novel mechanisms and innovative methods (e.g., gene or stem cell therapy) have been utilized to treat such patients. 61, 62, 63

**PATHOLOGY**

There are two basic electrophysiological mechanisms which have been proposed as initiation and perpetuation of AF (Figure 3.7). First, rapid ectopic activity may trigger and maintain AF. Second, sustained AF may depend on single or multiple electrical re-entrant circuits which results from shortening of effective refractory periods and from localized deceleration of intra-atrial conduction. In addition to initiation by electrical trigger beats, re-entry requires a susceptible substrate such as fibrosis. These mechanisms are not mutually exclusive. Rather, trigger activity and re-entry co-exist and influence vice versa, which provides a mechanistic based on progressive nature of the disease. In addition to electroanatomical mechanisms, genetic mutations as well as several loci associated with AF have been identified through analysis of rare monogenetic hereditary AF or using genomewide association studies, respectively. 64–68
Rapid ectopic activity and re-entry are key electrophysiological mechanisms of atrial fibrillation. The development of functional reentrant circuits requires a trigger (e.g., an ectopic beat) that initiates the arrhythmia. Atrial remodeling generates a structural substrate for reentry by altering ion channel function or by inducing fibrosis. The leading circle concept and the spiral wave hypothesis represent models of reentry. Remodeling may induce ectopic electrical discharges through changes in Ca²⁺ ion desposition and K⁺ current levels which result in trigger activity.

Abbreviations: DAD, delayed after depolarization, EAD: early after depolarization.

**FOCAL ELECTRICAL ACTIVITY**

Ectopic impulse is formed by localized discharges from electrical “pacemakers” which arises from an area other than the sinus node. In AF, pulmonary veins shows electrical activity that triggers the arrhythmia. It is characterized by an imbalance of cellular repolarizing and depolarizing ionic currents in the diastolic phase of the action potential which depends on the adrenergic tone. If diastolic depolarization increases, the cell reaches the premature action potential firing, and generates ectopic activity. Early or delayed after depolarizations (EAD or DAD) may depolarize a cell.
before the next expected normal action potential which causes premature action potential firing. Early after depolarization results from a prolongation of the action potential duration which is due to reduced repolarizing K⁺ currents. Delayed after depolarization is caused by spontaneous diastolic release of Ca²⁺ ions from the sarcoplasmic reticulum (SR), which is due to SR calcium overload or to dysfunctional Ca²⁺ release through channels in the sarcoplasmic reticulum.

Mechanisms of Re-entry

Molecular mechanisms of re-entry may be raised from mainly two different pathophysiological mechanisms. First, re-entry and the development of AF may based between cellular refractoriness and conduction velocity. If the refractoriness is short and the intercellular transmission of action potentials is slow then circulating impulses after a distinct single re-entry circuit will be increased. When the effective refractory period is prolonged the re-entrant circuit terminates but forcing the excitation wave front into tissue that is still refractory.

A second model (“spiral wave theory”), the re-entering wave front resembles a spiral or top that continuously and rapidly rotates around a central core. Spiral wave maintenance rotor activity depends on high cellular excitability and short atrial refractoriness. Rotor drifting activity across the atria occurs with slow rotation speed, de-stabilizing electrical and positional stability and promoting its termination when reaching refractory tissue.

Recent studies have been suggested a more complex mechanism of Atrial Fibrillation, which depends on patient-specific electrical and structural conditions of patients. Ectopic activity located at the junction between the pulmonary veins which are main sources and the left atrium have been revealed to initiate and perpetuate AF.
ELECTRICAL REMODELING

Evolving experimental and clinical evidence indicates that electrical and structural alterations referred to as atrial remodeling play an essential role in development and maintenance of AF. Remodeling may be caused either by concomitant cardiovascular disease or by the arrhythmia itself. The generation of electrical conditions and anatomical substrates that support slow conduction, shortening of atrial refractory periods, and electrical re-entry is mechanistically relevant. Electroanatomical substrates allow for generation of multiple re-entrant circuits, providing the basis for maintenance of persistent AF and stabilizing the arrhythmia. Action potential shortening and reduced refractoriness is associated with a reduction of L-type Ca²⁺ channel expression and up-regulation of inward rectifier (IK1) and acetylcholine-dependent K⁺ current (IK,Ach). Spatiotemporal changes in K⁺ ion channel expression that may occur with age or in response to cardiac disease including AF are particularly critical.²²–²⁴ Potassium channels determine atrial action potential duration and effective refractory periods, and both increased and reduced K⁺ channel activity can lead to atrial arrhythmia. The significance of potassium channel dysfunction is well documented for ventricular arrhythmias.⁷⁰,⁷¹ In addition, atrial fibrosis reduces conduction velocity locally, causes anisotropic conductivity, and represents an irreversible substrate for AF. Additional structural changes observed during AF include inflammatory reaction, amyloid deposit, apoptosis, necrosis redistribution of gap junctions, microvascular changes, and endocardial remodeling. The molecular mechanisms leading to electroanatomical remodeling remain incompletely understood.⁷²
AUTONOMIC NERVOUS SYSTEM

Cardiac electrophysiology is tightly regulated by the autonomic nervous system. The delicate balance between adrenergic and cholinergic stimulation influences the occurrence and maintenance of AF.\textsuperscript{73} Adrenergic activity and increased catecholamine levels trigger AF acutely and are associated with chronic AF, while β-blockers are effective in suppressing the arrhythmia. Furthermore, abnormal heart rate variability indicating disturbances of cardiac autonomic regulation was identified as an independent risk factor of AF, and vagosympathetic nerve stimulation has proven effective to reduce AF and to prevent and reverse atrial remodeling induced by cholinergic stimulation. Electrophysiological effects of adrenergic and cholinergic stimuli are mediated via regulation of multiple cardiac ion currents, including pacemaker current, L-type Ca\textsuperscript{2+} current, and multiple potassium ion channels.\textsuperscript{74, 75}

TREATMENT

Clinical classification

Atrial fibrillation tends to progress from short episodes to longer more frequent attacks and sustained forms of arrhythmia. Asymptomatic episodes are common, even in symptomatic patients. Five types of AF are clinically distinguished based on the duration of the arrhythmia:

1. First diagnosed \textit{AF} is present in patients who experience AF for the first time.
2. \textit{Paroxysmal AF} terminates spontaneously within less than 7 days after onset.
3. \textit{Persistent AF} extends beyond 7 days or requires termination by cardioversion.
4. \textit{Long-standing persistent AF} is diagnosed when persistent AF lasts 1 year.
5. The term *permanent AF* is used when the arrhythmia is accepted and no rhythm control strategy is followed.

Of note, the risk of thromboembolism does not depend on the duration of AF episodes. Thus, therapies aimed at preventing AF-related complications (e.g., stroke) are similarly required in all cases of AF.

**THERAPEUTIC CONCEPTS**

AF therapy focuses on symptom management and prevention of complications and may require treatment of concomitantis, hypertrophy cardiac or endocrine disease, control of cardiac rhythm and ventricular rate, and antithrombotic therapy (Figure 2). The successful treatment of primary causes is essential to suppress or eliminate AF. During AF, normal AV node conduction can lead to rapid ventricular rate response, resulting in impairment of left ventricular function and severe limitation of physical activity, which is a frequent cause for patient hospitalization. Rate control is usually achieved by pharmacological reduction of AV nodal conduction velocity until the ventricular heart rate is decreased to a less symptomatic state.

**CURRENT ANTIARRHYTHMIC DRUG THERAPY**

Conditions that increase classical antiarrhythmic therapy may shorten refractoriness and promote AF maintenance. The drugs which control rhythm suppress AF. However, the number of drugs available for rhythm control is limited. Classic antiarrhythmic Na\(^+\) current inhibitors (class I drugs) may decrease excitability and destabilize rotator activity. While K\(^+\) channel blocking (or class III) drugs suppress reentry mechanisms by extending action potential duration and repolarization. Class Ic agents increase mortality in patients with congenital heart disease, and amiodarone has an extensive side effect despite its efficiency in maintaining sinus rhythm. On top of that, amiodarone is the most commonly used
antiarrhythmic drug to achieve and maintain normal sinus rhythm. In addition, amiodarone has a heart rate lowering effect and simultaneously can be used to control heart rate, especially, if classic rate control agents failed or contraindicated. The amiodarone has limited use due to significant adverse effects including decreased blood pressure, skin discoloration, thyroid toxicity, corneal deposits, optic neuropathy pulmonary toxicity, and sinus bradycardia. Therefore, a significant number of patients are not eligible or refuse to take the drug.

Furthermore, control of rhythm by either of these compounds has not been exhibited to reduce patient mortality. Suppression of calcium currents by application of common drugs such as calcium channel blockers. Consequently, pharmaceutical research has been focused on the development of more favorable multichannel blocking agents as well as novel ion-channel and non-channel targets.\textsuperscript{7,9}
Fig 3.7 Overview: treatment options for patients with AF.

Abbreviations: ACE: angiotensin-converting enzyme, LAA: left atrial appendage, ARB, angiotensin receptor blocker.
RATE VS RHYTHM CONTROL

Comparative Studies of rate and rhythm control strategies (PIAF [Pharmacological Intervention in Atrial Fibrillation], AFFIRM [Atrial Fibrillation Follow-up Investigation of Rhythm Management], RACE [Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation], STAF [The Strategies of Treatment of Atrial Fibrillation], and HOT CAFE [How to Treat Chronic Atrial Fibrillation]) did not prove morbidity/mortality benefits. 76-80

These observations are counter intuitive considering severe complications and mortality associated with AF but may be characterized to pro arrhythmic side effects of antiarrhythmic drugs used for rhythm control. Clinically, the decision between rate or rhythm control based on multiple patient specific factors including hemodynamic effects, duration and frequency of AF episodes, underlying structural or endocrine disease, the severity of symptoms, and the outcome of previous treatment strategies.

PHARMACOLOGICAL AND DIRECT CURRENT CARDIOVERSION

Several episodes of atrial fibrillation terminate spontaneously within 24 to 48 hours. Irregular heart beat and ventricular rate associated with AF may require acute recovery of sinus rhythm in severely complexed patients. Acute conversion to NSR may achieve by direct current cardioversion (DCC). An immediate DCC should be performed in cases of hemodynamic instability. In (within less than 7 days) or In patients with persisting symptoms despite adequate rate control, pharmacological cardioversion may be useful in stable patients with recent onset AF (less than 7 days). Pharmacological cardioversion success rate is lower compared to direct current cardioversion, In which sedation or anesthesia is not required. For pharmacological cardioversion, continuous ECG monitoring are required compulsory to detect
ventricular arrhythmia, sinus node arrest and atrioventricular block. Pharmacological cardioversion include these drugs eg amiodarone, propafenone and flecainide.

**NOVEL ANTIARRHYTHMIC DRUGS**

Dronedarone is a novel antiarrhythmic drug that has been developed to provide rhythm and rate control in AF patients with lesser side effects as compared with amiodarone. Dronedarone is a congener of amiodarone but unlike amiodarone, it does not contain the iodine moieties affecting thyroid function. Moreover the addition of a methyl sulphonyl group reduces its lipophilicity and decreases its plasma half-life. Dronedarone is a multichannel blocker that meets criteria of all four Vaughan Williams anti-arrhythmic drug classes. \(^{81-83}\) Duration of action potential is prolonged, rate of the heart is reduced and the risk of torsade de pointes arrhythmias is decreased. Dronedarone significantly reduced the incidence of hospitalization due to cardiovascular events or death in high-risk AF patients. Liver function should be monitored as cases of severe liver damage.

**CATHETER ABLATION OF AF**

Catheter ablation has been become an established therapy modality in symptomatic AF patients. Interventional strategies of AF ablation is isolated though electrical triggers inside the pulmonary veins and suppress excitation wave mobility. These electrically isolated zones prevent re-entry and wavelet propagation by ablation of local areas of slow conduction in heart. \(^{84-87}\)

Circumferential pulmonary vein isolation using irrigated radiofrequency current is used to isolate ectopic electrical PV activity from the LA. Generally this technique for catheter ablation of AF is evolving rapidly to improve catheter manipulation, ablation efficacy, and procedural safety and contact force monitoring. Catheter ablation is generally used for patients with symptomatic AF despite
antiarrhythmic treatment. Clinically, left atrial size, previous therapy and concomitant cardiovascular disease should be considered in each individual patient. The recurrence rate in patients with paroxysmal AF is generally lower compared with persistent or permanent AF.\(^8\) Complications include pericardial thromboembolic events, vascular complications, pulmonary vein stenosis tamponade and pericarditis.

Esophageal injuries that based on energy settings and esophageal temperature as well as iatrogenic atrial septal defects caused by single-puncture, double transseptal approaches. Because of introduction of the technique the complication rate reduced while the success rate continuously increased owing to periprocedural safety measures and to improved operator experiences and skills.\(^89-90\)

**PREVENTION OF THROMBOEMBOLIC EVENTS IN ATRIAL FIBRILLATION**

Atrial fibrillation produces more complication of the risk of stroke. \(t\) Oral anticoagulation with vitamin K antagonists (VKA) is effective than aspirin for prevention of stroke in patients with AF.

Antithrombotic therapy are depends on patient specific evaluation of risk factors for systemic embolism and stroke. CHADS2 (cardiac failure, hypertension, age, diabetes, and stroke doubled) risk stratification scheme may be applied as initial and rapid tools of assessing the risk of embolism.\(^91, 92\)

**NEWER ANTICOAGULANT DUGS**

For laboratory monitoring, vitamin K antagonists are cumbersome to use which exhibit multiple interactions with food and drugs. Therefore significantly produce discontinuation rates. New oral anticoagulant agents are effective, safe and
convenient to use has attentioned primarily on direct thrombin inhibitors eg. dabigatran, rivaroxaban and apixaban. The RELY (Randomized Evaluation of Long-Term) anticoagulant therapy study demonstrated non inferiority of 110 mg BD dabigatran which may help prevention of stroke and systemic embolism with lower rates of major hemorrhage.\textsuperscript{93}

If, an extra dose 150 mg BD administered showed lower rates of embolism and similar incidence of hemorrhage which may prevent of thrombo embolism in AF patients. Recommended dosage is 150 mg BD of dabigatran may considered as an alternative to VKA therapy in USA. The apixaban (factor Xa inhibitor) is superior to aspirin in AF patients intolerant or unsuitable for VKA in the AVERROES (Apixaban versus Acetylsalicylic Acid (ASA) to Prevent Strokes) trial.\textsuperscript{94,95}

In year 2010, results of the Stroke Prevention using the Rivaroxaban (Oral Direct Factor Xa Inhibitor) when compared with Warfarin in Patients with Nonvalvular Atrial Fibrillation (ROCKET AF) trial were presented at the American Heart Association’s Scientific Sessions.\textsuperscript{96} This trial exhibited that rivaroxaban was as effective as warfarin in preventing stroke in AF patients and also have not increased their risk of bleeding.

**INTERVENTIONAL APPROACHES TO STROKE PREVENTION**

About 80\% of thrombo embolisms concerned with AF are caused by thrombi generating from the left atrial appendage. Occlusion of the left atrial appendage should be provided non-pharmacological alternative methods to reducing the risk of stroke in AF patients. However, during surgery LAA exclusion is not sufficiently supported by data and may even increase the risk of stroke when incomplete occlusion occurs.\textsuperscript{97,98}
Current studies of percutaneous transcatheter delivery of dedicated occlusion devices eg. are PLAATO system (withdrawn due to commercial reasons), WATCHMAN and AMPLATZER (cardiac plug) have produced encouraging results as alternatives to VKA in particular patients.\textsuperscript{99–103}

**UPSTREAM THERAPY**

Upstream therapy to inhibit myocardial remodeling adjacent with hypertension and heart failure may prevent the development of AF (primary prevention) and reduce recurrence hearts rates and progression to permanent AF (secondary prevention). Number of functional reentrant circuits is limited due to up streams therapy reduce left atrial size. It is also expected that upstream therapy may be prevent re-entry by deceleration of intercellular conduction velocity and by suppression of electrical ion channel remodeling. ACE inhibitors, Angiotensive receptor antagonist and statins may be considered for primary prevention in patients with concomitant structural heart disease.

**BIOLOGICAL ANTIARRHYTHMIC THERAPY**

Recent pharmacological therapy to treat AF is limited by reduced efficacy, side effects, and safety issues in a significant number of patients. Non-pharmacological therapy is improving, but only a limited number of patients can be treated by AF ablation. Gene therapy is novel treatment offers greater selectivity than small-molecule or interventional approaches.\textsuperscript{104, 105}
3.5 HERBAL MEDICINE FOR THE TREATMENT OF CARDIOVASCULAR DISEASE

Herbs have been an integral part of society since the beginning of human civilization and are valued for their culinary and medicinal properties. With the development of patented medicines in the early part of the 20th century, herbal medicine lost ground to the new synthetic medicines touted by scientists and physicians to be more effective and reliable. Nevertheless, herbal remedies are still popular in the United States. Herbal medicine, i.e., plant structures known as phytomedicinals or phytopharmaceuticals, has become an increasing presence and area of interest to both pharmacists and other health care professionals. In fact, herbal medicines have contributed to commercial drug preparations manufactured today, such as ephedrine from *Ephedra sinica* (ma-huang), digitoxin from *Digitalis purpurea* (foxglove), salicin (the source of aspirin) from *Salix alba* (willow bark), and reserpine from *Rauwolfia serpen-tina* (snakeroot). The discovery of the antineoplastic agent paclitaxel (Taxol) from *Taxus brevifolia* (the Pacific yew tree) stresses the role of plants as a continuing resource for modern medicine.

The following review of herbal medicines affecting the cardiovascular system is based on information gleaned from the scientific literature (Table 3.5). Most herbal medicinals have multiple cardiovascular effects.
Active components in herbal medicine have fewer side effects and toxicities in comparison with the concentration of active components in the allopathic medicines. However, cardiovascular disease is a serious health problem and no one should attempt to self medication with herbal remedies without first consulting with physician.

**CONGESTIVE HEART FAILURE**

**Cardiac Glycosides**

Several herbs contain potent cardio active glycosides that have positive inotropic effects on the heart. Best examples is digitoxin, derived from either *Digitalis purpurea* (foxglove) or *D. lanata*, and digoxin, derived from *D. lanata* alone, have

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**TABLE 3.5**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Examples of Herbs Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td><em>Digitalis purpurea</em></td>
</tr>
<tr>
<td></td>
<td><em>Digitalis lanata</em></td>
</tr>
<tr>
<td></td>
<td><em>Crataegus</em> species</td>
</tr>
<tr>
<td></td>
<td>Berberine</td>
</tr>
<tr>
<td>Systolic hypertension</td>
<td><em>Rauwolfia serpentine</em></td>
</tr>
<tr>
<td></td>
<td><em>Stephania tetrandra</em></td>
</tr>
<tr>
<td></td>
<td><em>Veratrum</em> alkaloids</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td><em>Crataegus</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Panax notoginseng</em></td>
</tr>
<tr>
<td></td>
<td><em>Salvia miltiorrhiza</em></td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Garlic</td>
</tr>
<tr>
<td>Cerebral insufficiency</td>
<td><em>Ginkgo biloba</em></td>
</tr>
<tr>
<td></td>
<td><em>Rosmarinus officinalis</em></td>
</tr>
<tr>
<td>Venous insufficiency</td>
<td><em>Aesculus hippocastanum</em></td>
</tr>
<tr>
<td></td>
<td><em>Ruscus aculeatus</em></td>
</tr>
</tbody>
</table>
been used in the treatment of congestive heart failure (CHF) for many decades. The dose of cardiac glycosides must be adjusted to the needs of each patient because of low therapeutic index. It is necessary to standardization of powdered digitalis, digitoxin, or digoxin. Nonstandardized herbal agents would be dangerous and foolhardy when treating of CHF patients. Common plant sources of cardiac glycosides include *D. purpurea* (foxglove, already mentioned), *Asclepias curassavica* (redheaded cotton bush), *Asclepias fruticosa* (balloon cotton), *Calotropis precera* (king’s crown), *Carissa acokanthera* (bushman’s poison), *Carissa spectabilis* (winter-sweet), *Apocynum cannabinum* (black Indian hemp), *Strophanthus hispidus* and *Strophanthus kombe* (stropho-thus), *Thevetia peruviana* (yellow oleander), and *Urginea maritima* (squill). *Cerbera manghas* (sea mango), *Cheiran-thus cheiri* (wallflower), *Convallaria majalis* (lily of the valley, convallaria), *Cryptostegia grandi-flora* (rubber vine), *Helleborus niger* (black helle-bore), *Helleborus viridus*, *Nerium oleander* (ole-ander), *Plumeria rubra* (frangipani), *Selenicereus grandiflorus* (cactus grandiflorus), *Adonis microcarpa* and *Adonis vernalis* (Adonis). Even the venom glands of the *Bufo marinus* (cane toad) contain cardiac glycosides.

**Berberine**

Berberine is an alkaloid distributed widely in nature and used in the Orient for the treatment of CHF; it is also reported to have antihypertensive and antiarrhythmic actions. In a recent placebo-controlled trial, patients with heart failure and significant ventricular ectopy on standard therapy received berberine 1.2 to 2.0 mg/day for up to 24 months.

**Rauwolfia Serpentina**

The root of *Rauwolfia serpentina* (snakeroot), the natural source of the alkaloid reserpine, has been a Hindu Ayurvedic remedy since ancient times. In 1931, Indian
literature first described the use of *R. serpentina* root for the treatment of hypertension and psychoses. Both standardized whole-root preparations of *R. serpentina* and its reserpine alkaloid are officially monographed in the *United States Pharmacopeia*.\(^{111}\) A 200- to 300-mg dose of powdered whole root taken orally is equivalent to 0.5 mg of reserpine.

Reserpine was one of the first drugs used on a large scale to treat systemic hypertension. It acts by irreversibly blocking the uptake of biogenic amines (norepinephrine, dopamine, and seroto-nin) in the storage vesicles of central and peripheral adrenergic neurons, thus leaving the catecholamines to be destroyed by the intraneuronal monoamine oxidase in the cytoplasm. The depletion of catecholamines accounts for reserpine’s sympatholytic and antihypertensive actions.

**Stephania Tetrandra**

*Stephania tetrandra* is sometimes used in Traditional Chinese Medicine (TCM) to treat hypertension. Tetrandrine, an alkaloid extract of *S. tetrandra*, has been shown to be a calcium-channel antagonist, paralleling the effects of verapamil. Tetrandrine inhibits T and L calcium channels, interferes with the binding of diltiazem and methoxyverapamil at calcium-associated sites, and suppresses aldosterone production. In addition to its cardiovascular actions, tetranderine has reported antineoplastic, immunosuppressive, and mutagenic effects.\(^{112}\)

**Lingusticum wallichii**

The root of *Lingusticum wallichii* (chuan-xiong, chuan-hsiung) is used in TCM as a circulatory stimulant, hypotensive agent, and sedative. Tetramethylpyrazine, the active constituent extracted from *L. wallichii*, inhibits platelet aggregation in vitro and lowers blood pressure by vasodilation in dogs. With its actions independent of the
endothelium, tetramethylpyrazine’s vasodilatory effect is mediated by calcium antagonism and nonselective antagonism of alpha adrenoceptors.\textsuperscript{113}

**Uncaria Rhynchophylla**

*Uncaria rhynchophylla* (gou-teng) is sometimes used in TCM to treat hypertension.\textsuperscript{112} Its indole alkaloids, rhynchophylline and hirsutine, are thought to be the active principles of *U. rhyn-chophylla*’s vasodilatory effect. The mechanism of *U. rhynchophylla*’s actions is unclear. Some studies point to an alteration in calcium flux in response to activation, whereas others point to hirsutine’s inhibition of nicotine-induced dopamine release. *U. rhyncho-phylla* extract appears to stimulate endothelium-derived relaxing factor/nitric oxide release without involving muscarinic receptors.\textsuperscript{114}

**Veratrum**

All *Veratrum* plants contain poisonous veratrum alkaloids, which are known to cause vomiting, bradycardia, and hypotension. Most cases of *Veratrum* poisonings are due to misidentification with other plants. Although once a treatment for hypertension, the use of *Veratrum* alkaloids has lost favor owing to a low therapeutic index and unacceptable toxicity, as well as the introduction of safer antihypertensive drug alternatives.

*Veratrum* alkaloids enhance nerve and muscle excitability by increasing sodium conductivity. They act on the posterior wall of the left ventricle and the coronary sinus baroreceptors, causing a reflex hypotension and bradycardia via the vagus nerve (Bezold–Jarisch reflex). Nausea and vomiting are secondary to the alkaloids’ actions on the nodose ganglion.\textsuperscript{113}

**Crataegus**

Hawthorn, a name encompassing many *Crataegus* species (such as *C. oxyacantha* and
Crataegus leaves, flowers, and fruits contain a number of biologically active substances such as oligomeric procyanidins, flavonoids, and cat-echins. From current studies, Crataegus extract appears to have antioxidant properties and can inhibit the formation of thromboxane A2. Also, Crataegus extract antagonizes the increases in cholesterol, triglycerides, and phospholipids in low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) in rats fed a hyperlip-idxemic diet; thus, it may inhibit the progression of atherosclerosis. According to one study, Crataegus extract in high concentrations has a cardio-protective effect on ischemic-reperfused heart without an increase in coronary blood flow. Double-blind clinical trials have demonstrated simultaneous cardiotropic and vasodilatory actions of Crataegus. In essence, Cratae-gus increases coronary perfusion, has a mild hypotensive effect, antagonizes atherosclerosis, has positive inotropic and negative chronotropic actions, and as an adjunct therapy, improves the symptoms of CHF.

Panax Notoginseng

Because of its resemblance to Panax ginseng (Asian ginseng), P. notoginseng (pseudoginseng; sanqui) has acquired the common name of pseudoginseng, especially since it is often an adulterant of P. ginseng preparations. In TCM, the root of P. notoginseng is used for analgesia and hemostasis. It is also often used in the treatment of patients with angina and coronary artery disease.

Another study suggests that P. notoginseng saponins may inhibit atherogenesis by interfering with the proliferation of smooth muscle cells. The role of P. notoginseng in the treatment of hypertension is less certain, since it causes
vasodilation or vasoconstriction depending on concentration and the target vessel.

**Salvia Miltiorrhiza**

*Salvia miltiorrhiza* (danshen), a relative of the Western sage *S. officinalis*, is native to China. In TCM, the root of *S. miltiorrhiza* is used as a circulatory stimulant, sedative, and cooling agent. *S. miltiorrhiza* may be useful as an anti-anginal agent because, like *P. notoginseng*, it has been shown to dilate coronary arteries in all concentrations. Also, *S. miltiorrhiza* has variable action on other vessels, depending on its concentration, so it may not be as helpful in treating hypertension\(^\text{113}\).

**ATHEROSCLEROSIS**

**Allium Sativum**

In addition to its use in the culinary arts, *Allium sativum* (garlic) has been valued for centuries in many cultures for its medicinal properties. In recent decades, animal and human data have focused on garlic’s use in treating atherosclerosis and hypertension. A number of studies have demonstrated garlic’s effects, which include lowering blood pressure, reducing serum cholesterol and triglycerides, enhancing fibrinolytic activity, and inhibiting platelet aggregation. However, some investigators have been hesitant to endorse the routine use of garlic for cardiovascular disease outright despite positive evidence because many of the published studies had methodologic short-comings. The pharmacologic properties of garlic are extremely complex, comprising a variety of sulfur-containing compounds that include allicin, alliin, diallyl di-sulfide, ajoene, s-allylcysteines, and gamma-glutamylpeptides, to mention a few. Many of the previous controlled trials of garlic used different preparations containing all or some of these active pharmacologic factors\(^\text{123-124}\).
CEREBRAL AND PERIPHERAL ARTERIAL DISEASE

**Ginkgo Biloba**

Dating back well over 200 million years, *Ginkgo biloba* (maidenhair tree) was apparently saved from extinction by human intervention, surviving in Far Eastern temple gardens while disappearing for centuries in the West. It was reintroduced to Europe in 1730 and became a favorite ornamental tree. Although the root and kernels of *G. biloba* have long been used in TCM, *Ginkgo* gained attention in the West during the 20th century for its medicinal value after a concentrated extract of *G. biloba* leaves was developed in the 1960s. At least two groups of substances within *G. biloba* extract demonstrated beneficial pharmacologic actions. The flavonoids reduce capillary permeability and fragility and serve as free-radical scavengers. The terpenes (i.e., ginkgolides) inhibit platelet activating factor, decrease vascular resistance, and improve circulatory flow without appreciably affecting blood pressure. Continuing research appears to support the primary use of *G. biloba* extract for treating cerebral insufficiency and its secondary effects on vertigo, tinnitus, memory, and mood. In addition, *G. biloba* extract appears to be useful for treating peripheral vascular disease, including intermittent claudication and diabetic retinopathy.125-126

**Rosmarinus Officinalis**

*Rosmarinus officinalis* (rosemary) is mentioned in several herbal sources as a tonic and all around stimulant. Traditionally, rosemary leaves are used to enhance circulation, elevate mood, aid digestion and boost energy.Externally application of volatile oils of rosemary are supposedly benefits for arthritic conditions and baldness.127

Some studies have been focused on antioxidant effects of diterpenoids, especially carnosic acid and carnosol which are isolated from rosemary leaves. In addition to
having antineoplastic effects (especially skin), antioxidants in rosemary have been credited with stabilizing erythrocyte membranes and inhibiting superoxide generation and lipid peroxidation. Essential oils of rosemary have been used as hyperglycemic, antimicrobial and insulin-inhibiting actions. Leaves of rosemary contain high amounts of salicylates. Its flavonoid pigment diosmin have been reported to decrease capillary permeability and fragility.\textsuperscript{128-131}

**VENOUS INSUFFICIENCY**

*Aesculus Hippocastanum*

The seeds of *Aesculus hippocastanum* (horse chestnut) have long been used in Europe to treat venous disorders such as varicose veins. The medicinal qualities of horse chestnut reside mostly in its large seeds, which resemble edible chestnuts. The seeds contain a complex mixture of saponins, glycosides, and several other active ingredients. The grouping of most interest is called aesculic acid or aescin. In addition to a high level of flavonoids, horse chestnuts contain several minerals including magnesium, manganese, cobalt, and iodine. The saponin glycoside aescin from horse chestnut extract (HCE) inhibits the activity of lysosomal enzymes, which are thought to contribute to varicose veins by weakening vessel walls and increasing permeability, resulting in dilated veins and edema.

*Ruscus Aculeatus*

Like *A. hippocastanum*, *Ruscus aculeatus* (butcher’s broom) is known for its use in treating venous insufficiency. *R. aculeatus* is a short ever-green shrub found commonly in the Mediterranean region. Two steroidal saponins, ruscogenin and neurogenin, extracted from the rhizomes of *R. aculeatus* are thought to be its active components.\textsuperscript{132} In vivo studies on hamster cheek pouch reveal that topical *Ruscus*
extract dose-dependently antagonizes a histamine-induced increase in vascular permeability. Moreover, topical *Ruscus* extract causes dose-dependent constriction on venules without appreciably affecting arterioles. Several small clinical trials using topical *Ruscus* extract support its role in treating venous insufficiency. Another small trial (*n* 18) showed that topical *Ruscus* extract may be helpful in reducing venous dilatation during pregnancy. Oral agents may be as useful as topical agents for venous insufficiency, although the evidence is less convincing.\textsuperscript{133-134}

**Non Cardiovascular Herbs With Adverse Cardiovascular Effects**

Herbs used to treat other condition can have adverse cardiovascular reaction (table 2)

**Tussilago Farfara**

*Tussilago farfara* (coltsfoot, kuan-dong-hua) is a perennial herb that is grown in many parts of northern China, Europe, Africa, Siberia, and North America. Over the years, *T. farfara* has acquired a reputation as a demulcent antitussive agent due to a throat soothing mucilage within the herb. Recently, the use of *T. farfara* has lost favor due to several studies that found senkirkine, a pyrrolizidine alkaloid known to cause hepatotoxicity, in all parts of the herb. In addition, rats fed a diet containing *T. farfara* had a high risk of developing hemangioendothelial sarcoma of the liver.\textsuperscript{135} A diterpene isolated from *T. farfara*, named tussilagone, is shown to be a potent respiratory and cardiovascular stimulant.

**Ephedra Sinica**

*Ephedra sinica* (joint fir, ma-huang), the natural source of the alkaloid ephedrine, has been used in TCM for over 5000 years as an antiasthmatic and decongestant. *Ephedra* has gained recent notoriety stemming from several fatalities of youths and professional athletes who took an excess of *Ephedra*, which is promoted by some as a
“legal high,” weight-loss aid, energy booster, and aphro-disiac. *Ephedra* alkaloids in dietary supplements caused 10 deaths and 13 permanent disabilities. Most of these tragic events were cardiovascular (e.g., cardiac arrest, arrhythmia) or neurologic (e.g., stroke, seizure).\textsuperscript{136}

Ephedrine increases mean, systolic, and diastolic blood pressures by vasoconstriction and cardiac stimulation. Ephedrine’s bronchodilating actions may be helpful for the chronic treatment of asthma. Ephedrine enhances the contractility of skeletal muscl

**Aconitum**

The roots of *Aconitum* species, such as *A. kus-nezoffii* (cao-wu) and *A. carmichaeli* (chuan-wa), are sometimes used in TCM to treat rheumatism, arthritis, bruises, and fractures. In Europe, *A. napellus* (monkshood, wolfsbane) grows in the wild and is sometime cultivated as an ornamen-tal.\textsuperscript{137}

Plant parts of *Aconitum* species contain diterpenoid ester alkaloids, including aconitine, which have been linked to several deaths in Hong Kong and Australia. Death usually results from cardiovascular collapse and ventricular tachyarrhythmias induced by aconite alkaloids. These alkaloids activate sodium channels and cause widespread membrane excitation in cardiac, neural, and muscular tissues. Characteristic manifestations of aconite intoxication include nausea, vomiting, diarrhea, hypersalivation, and generalized paresthesias (especially circumoral numbness). Musca-rinic activation may cause hypotension and bra-dyarrhythmias. Transmembrane enhancement of sodium flux during the plateau phase prolongs repolarization and induces afterdepolarizations and triggered automaticity in cardiac myocytes.
**Jin-Bu-Huan**

Often misidentified as a derivative of *Polygala chinensis*, jin-bu-huan is most likely derived from the *Stephania* genus. This herbal remedy contains an active alkaloid known as levotetrahydropalma-tine, which is a potent neuroactive substance that produces sedation, naloxone-resistant analgesia, and dopamine-receptor antagonism in animals. Jin-bu-huan is used as an analgesic, sedative, hypnotic, and antispasmodic agent as well as a dietary supplement.\(^{138}\)

**TABLE 3.6: Adverse Cardiovascular Reactions Observed with Herbal Medicines Used for Other Indications**

<table>
<thead>
<tr>
<th>Examples</th>
<th>Herbal Medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td><em>Tussilago farfara</em></td>
</tr>
<tr>
<td></td>
<td><em>Ephedra sinica</em></td>
</tr>
<tr>
<td>Hypotension</td>
<td><em>Aconitum</em> species</td>
</tr>
<tr>
<td>Digitalis toxicity</td>
<td>Over 20 herbal substances with activity to <em>digitalis</em> radioimmunoassay</td>
</tr>
<tr>
<td>Bradycardia</td>
<td><em>Aconitum</em> species</td>
</tr>
<tr>
<td></td>
<td>Jin-bu-huan</td>
</tr>
</tbody>
</table>
3.6 DIABETIC NEUROPATHY\textsuperscript{139-144}

Patients with diabetes mellitus may suffer from both acute and chronic complications. Acute complications concerned with ketoacidosis and ketoacidotic coma. Chronic complications can be classified into macrovascular and microvascular complications. Macrovascular diseases, predominantly myocardial infarction, CHF, and stroke. More than 75\% of diabetic mortality due to these complications. Microvascular abnormalities include diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy.

Diabetic neuropathy is the most common of diabetic complications up to 50\% of patients with type 1 or 2 disease have some form of neuropathy. Diabetic neuropathy is associated with progressive nerve fiber loss and both positive and negative clinical signs and symptoms such as pain, paresthesia, and loss of sensation.

3.6.1 Causes of Diabetic Neuropathy

The causes are probably different for different types of diabetic neuropathy. Researchers are studying how prolonged exposure to high blood glucose causes nerve damage. Nerve damage is likely due to a combination of factors:

- Metabolic factors, such as high blood glucose, long duration of diabetes, abnormal blood fat levels, and possibly low levels of insulin.
- Neurovascular factors, leading to damage to the blood vessels that carry oxygen and nutrients to nerves.
- Autoimmune factors that cause inflammation in nerves.
- Mechanical injury to nerves, such as carpal tunnel syndrome.
- Inherited traits that increase susceptibility to nerve disease.
- Lifestyle factors, such as smoking or alcohol use.
3.6.2 TYPES AND CLASSIFICATION

Diabetic neuropathy can be classified as peripheral, autonomic, proximal, or focal. Each affects different parts of the body in various ways.

- Peripheral neuropathy, the most common type of diabetic neuropathy, causes pain or loss of feeling in the toes, feet, legs, hands, and arms.
- Autonomic neuropathy causes changes in digestion, bowel and bladder function, sexual response, and perspiration. It can also affect the nerves that serve the heart and control blood pressure, as well as nerves in the lungs and eyes. Autonomic neuropathy can also cause hypoglycemia unawareness, a condition in which people no longer experience the warning symptoms of low blood glucose levels.
- Proximal neuropathy causes pain in the thighs, hips, or buttocks and leads to weakness in the legs.
- Focal neuropathy results in the sudden weakness of one nerve or a group of nerves, causing muscle weakness or pain. Any nerve in the body can be affected.

**Peripheral Neuropathy**

Peripheral neuropathy, also called distal symmetric neuropathy or sensorimotor neuropathy is nerve damage in the arms and legs. Feet and legs are likely to be affected before hands and arms. Many people with diabetes have signs of neuropathy that a doctor could note but feel no symptoms themselves. Symptoms of peripheral neuropathy may include

- numbness or insensitivity to pain or temperature
- a tingling burning or prickling sensation
- sharp pains or cramps
• extreme sensitivity to touch, even light touch
• loss of balance and coordination

These symptoms are often worse at night.

Peripheral neuropathy may also cause muscle weakness and loss of reflexes, especially at the ankle, leading to changes in the way a person walks. Foot deformities such as hammertoes and the collapse of the mid foot may occur. Blisters and sores may appear on numb areas of the foot because pressure or injury goes unnoticed. If an infection occurs and is not treated promptly the infection may spread to the bone, and the foot may then have to be amputated. Many amputations are preventable if minor problems are caught and treated in time.

**Autonomic Neuropathy**

Autonomic neuropathy affects the nerves that control the heart, regulate blood pressure, and control blood glucose levels. Autonomic neuropathy also affects other internal organs, causing problems with digestion, respiratory function, urination, sexual response, and vision. In addition, the system that restores blood glucose levels to normal after a hypoglycemic episode may be affected, resulting in loss of the warning symptoms of hypoglycemia.

**Proximal neuropathy**

Proximal neuropathy, sometimes called Lumbosacral plexus neuropathy, femoral neuropathy, or diabetic amyotrophic starts with pain in the thighs, hips, buttocks, or legs, usually on one side of the body. This type of neuropathy is more common in those with type 2 diabetes and in older adults with diabetes. Proximal neuropathy causes weakness in the legs and the inability to go from a sitting to a standing position without help. Treatment for weakness or pain is usually needed.
The length of the recovery period varies, depending on the type of nerve damage.

**Focal neuropathy**

Focal neuropathy appears suddenly and affects specific nerves, most often in the head, torso or leg. Focal neuropathy may cause.

- inability to focus the eye
- double vision
- aching behind one eye
- paralysis on one side of the face, called Bell’s palsy
- severe pain in the lower back or pelvis
- pain in the front of a thigh
- pain in the chest, stomach, or side
- pain on the outside of the shin or inside of the foot
- chest or abdominal pain that is sometimes mistaken for heart disease, a heart attack, or appendicitis.

Focal neuropathy is painful and unpredictable and occurs most often in older adults with diabetes. However it tends to improve by itself over weeks or months and does not cause long-term damage.
### Table 3.7

<table>
<thead>
<tr>
<th>Three classification systems for diabetic neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Clinical classification of diabetic neuropathies</strong></td>
</tr>
<tr>
<td>Polyneuropathy</td>
</tr>
<tr>
<td>Sensory</td>
</tr>
<tr>
<td>• Acute sensory</td>
</tr>
<tr>
<td>• Chronic sensorimotor</td>
</tr>
<tr>
<td>Autonomic</td>
</tr>
<tr>
<td>• Cardiovascular</td>
</tr>
<tr>
<td>• Gastrointestinal</td>
</tr>
<tr>
<td>• Genitourinary</td>
</tr>
<tr>
<td>• Other</td>
</tr>
<tr>
<td>Proximal motor (amyotrophy)</td>
</tr>
<tr>
<td>Truncal</td>
</tr>
<tr>
<td><strong>B. Patterns of neuropathy in diabetes</strong></td>
</tr>
<tr>
<td>Length-dependent diabetic polyneuropathy</td>
</tr>
<tr>
<td>• Distal symmetrical sensory polyneuropathy</td>
</tr>
<tr>
<td>• Large fibre neuropathy</td>
</tr>
<tr>
<td>• Painful symmetrical polyneuropathy</td>
</tr>
<tr>
<td>• Autonomic neuropathies</td>
</tr>
<tr>
<td>Focal and multifocal neuropathies</td>
</tr>
<tr>
<td>• Cranial neuropathies</td>
</tr>
<tr>
<td>• Limb neuropathies</td>
</tr>
<tr>
<td>• Proximal diabetic neuropathy of the lower limbs</td>
</tr>
<tr>
<td>• Truncal neuropathies</td>
</tr>
<tr>
<td>Non-diabetics neuropathies more common in diabetes</td>
</tr>
<tr>
<td>• Pressure palsies</td>
</tr>
<tr>
<td>• Acquired inflammatory demyelinating polyneuropathy</td>
</tr>
<tr>
<td><strong>C. Classification of diabetic neuropathy</strong></td>
</tr>
<tr>
<td>Rapidly reversible</td>
</tr>
<tr>
<td>• Hyperglycaemic neuropathy</td>
</tr>
<tr>
<td>Generalised symmetrical polyneuropathies</td>
</tr>
<tr>
<td>• Sensorimotor (chronic)</td>
</tr>
<tr>
<td>• Acute sensory</td>
</tr>
<tr>
<td>• Autonomic</td>
</tr>
<tr>
<td>Focal and multifocal neuropathies</td>
</tr>
<tr>
<td>• Cranial</td>
</tr>
<tr>
<td>• Thoracolumbar radiculoneuropathy</td>
</tr>
<tr>
<td>• Focal limb</td>
</tr>
<tr>
<td>• Proximal motor (amyotrophy)</td>
</tr>
<tr>
<td>Superimposed chronic inflammatory demyelinating neuropathy</td>
</tr>
</tbody>
</table>
3.6.3 SIGNS AND SYMPTOMS

In humans

Symptoms of nerve damage may include

- numbness, tingling, or pain in the toes, feet, legs, hands, arms, and fingers
- wasting of the muscles of the feet or hands
- indigestion, nausea, or vomiting
- diarrhea or constipation
- dizziness or faintness due to a drop in blood pressure after standing or sitting up
- problems with urination
- erectile dysfunction in men or vaginal dryness in women
- Weakness.

In animals

- Diabetic rats display a range of abnormal behavioral responses to nociceptive stimuli suggesting the presence of hyperalgesia. These include, reduced paw withdrawal thresholds to mechanical stimuli, reduced time to tail-flick after thermal stimulation and increased flinch responses following the injection of formalin into the paw.
- The emerging interest in these models has prompted a growing appreciation of the mechanisms of normal pain perception (nociception) and abnormal persistent pain following anerve injury (neuropathic pain) which in turn has ed o the application of similar tests to animal models of diabetes. Such studies show that diabetic rodents display physiologic , neurochemical, and behavioral indices suggestive of altered pain
perception which may make them useful for investigating etiologic mechanisms linking hyperglycemia with painful neuropathy.

Table 3.8: Signs and Symptoms in diabetic neuropathy

<table>
<thead>
<tr>
<th>LARGE FIBER</th>
<th>SMALL FIBRE</th>
<th>MOTOR</th>
<th>AUTONOMIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td><strong>Symptom</strong></td>
<td><strong>Symptom</strong></td>
<td><strong>Symptom</strong></td>
</tr>
<tr>
<td>Numbness, pin sand needles, tingling, poor balance</td>
<td>Pain; burning, shock like, stabbing allodynia, prickling, shooting.</td>
<td>Cramp, weak grip, twitching, foot drop</td>
<td>Decreased or increased sweating, dry eyes, mouth, erectile dysfunction, gastro paresi, faintness</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td>Decreased pin prick, temperature sensation</td>
<td>Reduced strength reflexes</td>
<td>Orthostasis, unequal pupil size</td>
</tr>
</tbody>
</table>

3.6.4 MOLECULAR MECHANISM BEHIND DIABETIC NEUROPATHY

**Advanced glycation products**

Non enzymatic reactions between reducing sugars and proteins result in advanced glycation end products (AGEs). Three main pathways are responsible for the formation of reactive dicarbonyls (AGE precursors)

- Oxidation of glucose to form glyoxal.
- Degradation of Amadori products (fructose-lysine adducts) and
- Aberrant metabolism of glycolytic intermediates to methylglyoxal.
Glycation end products and reactive dicarbonyls are heterogeneous modified extracellular and intracellular bimolecular components. Intracellular protein, both protein and DNA adducts alter function and cellular transport. Methyl glyoxal, a highly reactive dicarbonyl (AGE precursors), is exhibited to induce sensitivity to vascular damage in endothelial cells. Outside cell (extracellular) protein AGES include plasma and matrix proteins that disrupt cellular adhesion and activate the receptor for AGES (RAGE). AGE–RAGE receptor interaction activates the transcription factor nuclear factor kappa B (NF-κB). This transcript nuclear factor NF-κB regulates a number of intracellular activities including inflammation and apoptosis. This events activate of neuronal RAGE induces oxidative stress through NADPH oxidase activity.
Diabetic RAGE knockout mice (transgenic animals) showed significant development in DPN and diminished expression of NF-κB and PKC compared to wild type diabetic model. The biochemical damage induced by AGEs results in impaired nerve blood flow and diminished neurotrophic support.\textsuperscript{145}

**Fig.3.9** Advanced glycation end products.

**Oxidative stress**

- The AGE, polyol, hexosamine, PKC, and PARP pathways all contribute to neuronal damage illustrates that the AGE and polyol pathways directly alter the redox capacity of the cell either through direct formation of ROS or by depletion of essential components of glutathione recycling. Hexosamine, PKC, and PARP pathways showed damage through expression of inflammation proteins.
Axons are susceptible to hyperglycemic damage both due to their direct access to nerve blood supply and their large population of mitochondria (Mt). Mounting evidence suggests that the hyperglycemic environment coupled with a compromised blood supply overloads the metabolic capacity of the Mt, producing oxidative stress. This oxidative stress leads to Mt damage followed by axonal degeneration and death. Mitochondrial damage occurs due to excess formation of ROS and reactive nitrogen species (RNS).

ROS, such as superoxide and hydrogen peroxide, are produced under normal conditions through the Mt electron transport chain and are normally removed by cellular detoxification agents such as superoxide dismutase, catalase, and glutathione. Hyperglycemia leads to increased Mt activity, raising ROS production in the Mt. Peroxynitrite, the primary RNS, is formed by the reaction of superoxide and nitric oxide (NO). RNS induces a number of cytotoxic effects including protein nitrosylation and activation of PARP.

**Polyol pathway**

- An increase in the activity of the polyol pathway is one of the major metabolic contenders for the etiology of diabetic neuropathy, which include the formation of advanced glycation end product, the alteration of essential fatty acid metabolism and the abnormalities of neurotrophic factors\textsuperscript{146}.

- In polyol pathway, glucose is converted into sorbitol by Aldose Reductase (AR) and sorbitol dehydrogenase oxidises, sorbitol to fructose Niacinamide Adenosine Dihydrogen Phosphate (NADPH) is consumed by aldose reductase-mediated reduction of glucose to sorbitol (and NADPH is required for regeneration of antioxidant enzyme glutathione (GSH) thus deficient amount of glutathione contributes to oxidative stress (Moreover, conversion of
glucose to sorbitol induced osmotic stress and to restore osmotic equilibrium to cell, other osmolytes, particularly taurine and myo-inositol, are effluxes from cells.

- Depletion of taurine and myo-inositol in nerve cells are implicated in PDN and supplementation of taurine and myo-inositol prevented neuropathic deficits. On the other hand, excess formation of fructose in polyol pathway promotes advanced glycation end product as well as depletes NADPH, further augmenting Reactive Oxygen Species (ROS) mediated. Numerous agents have been evaluated over the past 20 years but most have not been licensed because of serious adverse events (tolrestat, zenarestat) or a lack of efficacy (ponalrestat, zenarestat).

Fig.3.10 polyol pathway is one of the major metabolic contenders for the etiology of diabetic neuropathy.
Hexosamine pathway

- Shunting of excess intracellular glucose into the hexosamine pathway might also cause several manifestations of diabetic complications. In this pathway, fructose-6-phosphate is diverted from glycolysis to provide substrates for reactions that require UDP-N-acetylglucosamine, such as proteoglycan synthesis and the formation of O-linked glycoproteins. Inhibition of the rate-limiting enzyme in the conversion of glucose to glucosamine — glutamine: fructose6-phosphateamidotransferase (GFAT) — blocks hyperglycaemia-induced increases in the transcription of TGF-a, TGF-b1 and PAI-1.

Growth factors

- Increasing evidence exists that there is a deficiency of growth factors such as nerve growth factor (NGF) in diabetes, as well as the dependent neuro peptides substance P and calcitonin gene-related peptide, and that this contributes to the clinical perturbations in small fiber function^{147}.

Schwann Cell

- Nerve injury resulting from diabetes mellitus is characterized by marked changes in Schwann cells and the axons sheath. The most obvious structural manifestation of diabetic neuropathy is a loss of both large and small nerve fibers, which is a prominent feature of chronic human and long-duration experimental diabetic neuropathy.
- While fiber loss is most prominent distally, particularly in the dorsal roots. Characteristic degenerative changes of unmyelinated fibers include shrinkage of axons, accumulation of enlarged vesicular elements and deterioration of tubular and filamentous elements of the cytoskeleton.
• Both primary segmental demyelination and demyelination secondary to axonal degeneration were documented in the same nerve biopsy. Demyelination has also been observed in long-term experimental diabetes Myelin defects, such as splitting and ballooning of the sheath, that appear to preceded myelination have been documented in the dorsal and ventral roots in rodent models of experimental diabetes and also in nerves of cats with spontaneously occurring diabetes.

• Paranodal swelling is thought to precede paranodal demyelination and to be associated with axo-glial dysjunction, the loss of the junctional contacts between paranodal Schwann cell loops and the axolemma on either side of the node of Ranvier. However, the existence of paranodal swelling and axo-glial dysjunction is contentious because, although repeatedly documented by some in experimental and human diabetic neuropathy others (have not detected these abnormalities\textsuperscript{148-149}.

A common element linking hyperglycemia induced damage

• Although specific inhibitors of aldose reductase activity, AGE formation, PKC activation and the hexosamine pathway each ameliorate various diabetes induced abnormalities in cell culture and animal models, there has been no apparent common element linking the four mechanisms of hyper glycaemia-induced damage.

This mechanism concerned that a single hyper glycaemia induced process excessive production of superoxide by the mitochondrial electron-transport chain. Several studies have proved that diabetes and hyperglycaemia increase oxidative stress but neither the underlying mechanism nor the consequences for other pathways of hyper glycaemic damage was proved\textsuperscript{145}. 

\textbf{Review of Literature}
3.7 DIAGNOSIS

- Although challenging, DPN can be diagnosed, classified, and managed on the basis of the patient’s history and results of a thorough physical examination.
- Systematic electrophysiological testing is not necessary in diabetic patients with typical peripheral neuropathy. Changes in conduction velocity can be detected in asymptomatic patients, but their presence is not predictive of the onset of symptomatic neuropathy.
- In addition, DPNP does not correlate with nerve conduction velocity, and the diagnosis of DPNP does not require evidence of a large-fiber abnormality. If motor signs are noted on the clinical examination (weakness during muscle testing), referral to a neurologist for electro diagnostic testing is certainly warranted.
- Although the initial recognition of neuropathy may be clinically confirmed by the relative loss of sharp vs light touch discrimination over the distal lower extremities during the physical examination, the use of the 10-g Semmes-
Weinstein monofilament permits more careful assessment for pressure perception. The nylon filament is gently pressed against the skin until it just buckles, generating the equivalent of 10 g of force.

- The sensitivity for predicting feet at risk of ulceration ranges from 100% cross sectional studies using the Semmes-Weinstein monofilament.15 Pressure perception assessments are usually taken at the hallux and metatarsal heads I, III, and V, although there is uncertainty regarding the necessity for multiple measurements.

- No consensus exists on whether 1, 2, or more abnormal measurements constitute a diagnosis of neuropathy.

- The absence of symptoms should not be equated with the absence of neuropathy; up to 50% of patients with DPN may be asymptomatic but are still at risk of foot ulcers. Therefore, monitoring for neuropathy should be a regular part of the clinical care of patients with DM.47 Such monitoring should include assessment with a 128-Hz tuning fork to check for vibration sensation, a broken tongue depressor to check for sharp sensation, test tubes that contain warm or cold water to evaluate temperature sensation, the10 monofilament to check pressure sensation, and cotton wool to check light touch sensation and the presence of abnormal pain responses from non painful stimuli.

### 3.8 DIFFERENTIAL DIAGNOSIS

- Conditions that should be considered and ruled out as sources of neuropathy or pain include malignant disease, toxic causes (eg, alcohol), and infections, particularly human immunodeficiency virus. The patient’s history may suggest other diagnoses as well, such as post herpetic neuralgia.
Other pain syndromes that may mimic DPNP include tarsal tunnel syndrome, osteoarthritis, idiopathic distal small fiber neuropathy, and erythromelalgia.

3.9 MANAGEMENT

3.9.1 Preventive treatment

- Prevention of diabetic neuropathy and its complications remains the best strategy. Optimum glycaemic control diminishes the risk of developing a disabling peripheral neuropathy, but carries an increased risk of hypoglycemia.
- Patients with diabetes also need advice about foot care and footwear, and about protection of hyposensitive areas and pressure points, to prevent the occurrence of painless ulcers and decrease the risk of bone infection. Prevention and treatment of the ‘diabetic foot’ are best administered in specialized foot clinics. Pancreas transplantation, which might stabilize then Neuropathy, is not yet routinely performed.

3.9.2 Pharmacological therapy

- However there is no particular or specific drug available for the diabetic neuropathic condition till date.
- The traditional analgesic ladder described by the World Health Organization (WHO) is of limited usefulness in the treatment of neuropathic pain. This is because simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are often less effective in neuropathic pain (although, as mentioned above, they may have a role in the treatment of inflammatory ‘flare-ups’).
Table 3.9: The ABCs of diabetic neuropathy management

<table>
<thead>
<tr>
<th>A</th>
<th>Antidepressants, anticonvulsants, topical anesthetics are the first-line treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Blood sugar management</td>
</tr>
<tr>
<td>C</td>
<td>Cardiovascular risk factor reduction</td>
</tr>
<tr>
<td>D</td>
<td>Diet and exercise for weight management</td>
</tr>
<tr>
<td>E</td>
<td>Emerging therapies for diabetes and neuralgia</td>
</tr>
<tr>
<td>F</td>
<td>Foot care to reduce infections and amputations</td>
</tr>
</tbody>
</table>

Table 3.10

Drugs which are commonly prescribe in neuropathic pain

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
<th>Mechanism of action</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptics</td>
<td>Lamotrigine</td>
<td>Blockade of sodium and calcium channel</td>
<td>Blurred vision, ataxia, pruritis, somnolence, peripheral edema, anorexia, agitation &amp; irritability</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zonisamide</td>
<td>Free radical scavenging property</td>
<td></td>
</tr>
<tr>
<td>Antidepressant</td>
<td>Trazodon,</td>
<td>Blockade of serotonin (5-HT)</td>
<td>Constipation, ataxia, dry mouth, insomnia,</td>
</tr>
<tr>
<td></td>
<td>Nefazodone,</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Review of Literature

<table>
<thead>
<tr>
<th></th>
<th>Vaniafaxine</th>
<th>Rupture pump, Down regulation of 5-HT$<em>A_1$ auto receptor, Down regulation of postsynaptic 5HT$</em>{2A}$ receptors</th>
<th>seizures, dizziness, hot flashes, Urinary retention, weight gain, arrhythmia.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids</strong></td>
<td>Morphine, Hydromorphone, Fetanyl, levophanol, Methadone</td>
<td>NMDA receptor antagonist and inhibits the reuptake of NE and 5-HT</td>
<td>Drowsiness, sedation, constipation, dizziness, nausea/vomiting</td>
</tr>
</tbody>
</table>

- In focal neuropathy, including cranial nerve palsy, PDN and truncal neuropathy, the disease course is self-limited, with spontaneous recovery within a few months in most cases. Control of pain can be difficult both in LDDP and in focal neuropathies. Carbamazepine, phenytoin, clonazepam, or paracetamol in combination with codeine phosphate can be useful.

- Tricyclic antidepressants, such as imipramine or amitriptyline, are often effective; the usual dose varies from 30-150 mg per day. Tricyclic antidepressants might aggravate postural hypotension. The recently introduced drugs duloxetine and pregabalin are also useful.

Non pharmacological devices can be used if a successful therapy could be identified Since there will be no interaction with the devices.
Table 3.11

Herbal drug used in the management Diabetic neuropathy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo biloba</td>
<td>Blocks induction of inducible nitric oxide synthase (iNOS) and release of nitric oxide (NO)</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>Inhibit the voltage-gated Na⁺ channels</td>
</tr>
<tr>
<td>Ocimum sanctum</td>
<td>Decreases the oxidative stress and calcium levels</td>
</tr>
<tr>
<td>Acorus calamus</td>
<td>Decreases the oxidative stress and calcium levels</td>
</tr>
<tr>
<td>Emblica officinalis</td>
<td>Inhibits lipid peroxidation and restore antioxidant enzymes</td>
</tr>
<tr>
<td>Combination of Psidium guajava, Momordica charantia and Cocculia Indica</td>
<td>Inhibits protein kinase C and act as antioxidant</td>
</tr>
</tbody>
</table>

3.9.3 Physical Therapy

Physical therapy can be beneficial and alternative treatment option for with diabetes patients. This may decrease dependency on pain relieving drug treatments. Some physiotherapy advance techniques can be help for alleviate symptoms brought on from diabetic neuropathy such as deep pain in the feet and legs, tingling or burning sensation in extremities, muscle cramps, muscle weakness and diabetic foot.

3.9.4 Specific therapy

Antioxidants: Evidence exists to suggest that during hyperglycemia glucose metabolism leads to generation of free radicals which affects endothelial function and vascular activity. In a animal study alpha lipoid acid has been showed promising results. Vitamin C is hypothesized to reduce cellular levels of reactive oxygen species.
and increase the level of nitrogen oxide similar to that of alpha lipoid acid. Vitamin C decreases plasma free radicals and increases levels of reduced glutathione and nitrogen oxide mediated vasodilatation.

3.10 MECHANISM OF STREPTOZOTOCIN CAUSING DIABETIC NEUROPATHY

- Streptozotocin is approved by the U.S. Food and Drug Administration (FDA) for treating metastatic cancer of the pancreatic islet cells. Since it carries a substantial risk of toxicity and rarely cures the cancer, its use is generally limited to patients whose cancer cannot be removed by surgery.
- The molecular weight of STZ is 265g/mol and the structure is composed of nitrosourea moiety with a methyl group attached at one end and a glucose molecule at the other end. Streptozotocin (STZ) (2-deoxy-2-[(methyl (nitroso)amino|carbonyl]amino)-β-D-glucopyranose) is a naturally occurring compound, produced by the bacterium Streptomyces achromogenes, that exhibits broad spectrum antibacterial properties.

3.10.1 Beta cell selectivity of streptozotocin

- The toxic action of streptozotocin and chemically related alkylating compounds requires their uptake into the cells. Nitrosoureas are usually lipophilic and tissue uptake through the plasma membrane is rapid; however,
as a result of the hexose substitution, streptozotocin is less lipophilic. Streptozotocin is selectively accumulated in pancreatic beta cells via the low-affinity GLUT2 glucose transporter in the plasma membrane.

- Thus, insulin-producing cells that do not express this glucose transporter are resistant to streptozotocin. This diminishes cellular NAD\(^+\), and subsequently ATP, stores.

- The depletion of the cellular energy stores ultimately results in beta cell necrosis. Although streptozotocin also methylates proteins, DNA methylation is ultimately responsible for beta cell death, but it is likely that protein methylation contributes to the functional defects of the Beta cells after exposure to streptozotocin. Inhibitors of poly ADP-ribosylation suppress the process of DNA methylation.

3.10.2 Mechanism of beta cell death\(^{158-160}\)

- Mode of Beta cell death result Chemical diabetes cells than MNU and methyl methanesulphonate has been taken as support for the notion that in insulin producing cells, as in other cell types, the mechanism of toxic action is due to alkylation, with methylation of DNA bases being more toxic than ethylation.

- Nitric oxide (NO) donor. Both streptozotocin and MNU contain a nitroso group and can liberate NO. In fact, streptozotocin has been shown to increase the activity of guanylyl cyclase and the formation of cGMP, which are characteristic effects of NO.

- In addition to STZ-induced cytotoxicity through DNA alkylation, reactive oxygen species, including superoxide (O\(^2^-\)), hydrogen peroxide (H\(_2\)O\(_2\)), hydroxyl radical (HO\(^•\)), and nitric oxide (NO\(^•\)), play a critical role in the mechanism of DNA damage and cytotoxicity of STZ. Streptozotocin is
cytotoxic to pancreatic β-cells and effects can be seen within one hour after administration.

- Types of DNA lesions formed by STZ include mono adducts, single and double stranded breaks, and alkali-labile sites. Severe DNA damage by STZ results in cell death by apoptosis or necrosis. Diabetic individuals and experimental animals exhibit high oxidative stress due to persistent and chronic hyperglycemia, thereby depleting the activity of oxidative defense system, and thus promoting de novo free radical generation. Oxidative stress has recently been shown to be responsible, at least in part, for pancreatic β-cell dysfunction caused by glucose toxicity.

- Under hyperglycemia production of various reducing sugars, such as glucose-6-phosphate and fructose, increases through glycolysis and polyol pathways. During this process, reactive oxygen species (ROS) are produced and cause tissue damage.

- So, STZ is widely employed to induce experimental diabetes in animals. Administration of a single dose of STZ (40 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg and 65 mg/kg i.p. or i.v.) in rats results in hyperglycaemia within 72 hours. STZ treatment causes significant increases in lipid peroxidation (MDA) and nitric oxide (NO) generation, and decreases antioxidant enzymes such as catalase, Glutathione peroxidase, and superoxide dismutase activities as well as pancreatic insulin contents when compared with the control animals in experiments. Decreases in antioxidant activities, and simultaneous increases in MDA and NO Activities, reflect susceptibility of pancreas to STZ’s significant oxidative stress.
3.11 Animal Models of diabetic neuropathy \textsuperscript{161-162}

3.11.1 In Vivo Animal Models

In vivo animal models for diabetic neuropathy studies can be subdivided into two groups: induced models and genetic models that mimic either type 1 (insulin dependent) or type 2 (insulin resistant) diabetes. In addition, other tissue-specific transgenic models can be rendered diabetic to study a specific pathway that might be involved in the pathogenesis.

- Diabetic neuropathy in type 1 diabetic models
- Diabetic neuropathy in type 2 diabetic models (Zucker diabetic fatty (ZDF) rat)
- The NOD mouse
- Otsuka Long-Evans Tokushima fatty (OLETF) rat
- Goto Kakizaki (GK) rat
- ob/ob mouse
- db/db mouse
- Transgenic mice expressing fluorescent sensory/motor neurons (thy-YFP)
- Transgenic and knockout models in other pathways regulating insulin action
- Transgenic mice lacking peripheral axonal neuro filaments (Nf-H-lacZ).
PLANTS PROFILE

3.12 CAESALPINIA PULCHERRIMA (L.) SWART

**Botanical name:** *Caesalpinia pulcherrima* (L.) Swartz.

**Common vernacular Names:**
- **English:** Flower fence, Peacock’s pride, Paradise flower, Pride of Barbados
- **Hindi:** Guletura
- **Telugu:** Ratnagandhi
- **Kannada:** Kenjige
- **Sanskrit:** Sidhakaya

**Scientific Classification:**
- **Kingdom:** Plantae - plants
- **Subkingdom:** Tracheobionta – Vascular plants
- **Super division:** Spermatophyta – Seed plants
- **Division:** Magnoliophyta – Flowering plants
- **Class:** Magnoliopsida – Dicotyledons
- **Subclass:** Rosidae
- **Order:** Fabales
- **Family:** Fabaceae
- **Genus:** *Caesalpinia* L. – nicker
- **Species:** *Caesalpinia pulcherrima* (L.) Sw.
Plate No.1: *C. Pulcherrima* stem

Plate No.2: *C. Pulcherrima* Bark

Plate No.3: *C. Pulcherrima* Leaves

Plate No.4: *C. pulcherrima* Flower

Plate No.5: *C. Pulcherrima* Fruit & seeds
MORPHOLOGY: \(^{163-164}\)

**Nature:** - Showy, very attractive, erect shrub or small tree, its height about 2-4 meters (13ft), with prickly branches, flowering all year.

**Stem:** - The stem and branches are armed with spines. The yellow, red, pink and orange flowers grow at the end of the prickly branches.

**Leaves:** - The leaves are bipinnate, 15-45 cm long, productive 2-10 pairs of pinnae.

**Flowers:** - The red, orange, yellow and pink flowers grow at the end of the prickly branches. The flowers are yellow, orange or red petals. The fruit is a pod 6-12 cm long.

**Fruits:** - A flat pod, 8-12 cm long 4 – 6 seeded dehiscent pods; Seeds oval, brown and compressed.

FOLKLORE/TRADITIONAL USES: \(^{165-166}\)

In folk medicine, various parts of *Caesalpinia pulcherrima* are used medicinally.

- A combination of the roots, bark, and leaves may be boiled into a medicinal tea, which is given to patients as a treatment for fever, jaundice, kidney disease, and gastrointestinal disorders. Gargling with the tea is also said to treat sores in the mouth or throat.

- Root, leaf, flower and seed used variously in indigenous medicines – for stomachache, gall bladder problems, kidney stones, to accelerate childbirth, as an abortifuge, among other ailments.

- Studies have indicated that this plant may be effective in assisting with weight loss.

- **Root:** A decoction is prescribed in intermittent fevers.
• **Bark:** emmenagogue, abortifacient.

• **Leaves:** A liquid extracted from the flowers of the plant is often used topically as an eye wash or applied to the body as an insecticide. It is used as laxative, antipyretic. In Eastern India it is used as a substitute for senna. Dried and powdered leaves are used in erysipelas. The liquid is sometimes consumed to treat a variety of other conditions. Patients with severe gastrointestinal disorders, including gastric ulcers, dysentery or severe diarrhea, and is also used against kidney stones, malarial fever and bronchitis, cancer. It also has antioxidant property.\(^{168}\)

• **Flowers:** Anthelmintic, also used for cough and catarrh. The juice from the flower cures sores.

• **Fruits:** Fruit of the plant, which is said to have astringent properties, to eat. These properties help the plant to dry out the intestinal tract.

• **Green seeds:** seeds cure bad cough, breathing difficulty, and chest pain may be eaten cooked, when ripe yield tannin and yellow (with alum) or black (with iron) dye.

**REPORTED CONSTITUENTS OF CAESALPINIA PULCHERRIMA:**

• **Peltocynoids and Homoisoflavonoids from caesalpinza pulcherrima.**

  *Pherson DMC, et al.,1983* isolated two new peltogynoids viz., pulcherriminand 6methoxypulcherrimin and two homoisoflavonoids, the recently reported compound bonducellin and a new derivative 8-methoxy-bonducellin from the stem part of Caesalpinia pulcherrima.\(^{167}\)

• **Diterpenoids from Caesalpinia pulcherrima.**
Pherson DMC et al., 1986 isolated three new furanoditerpenoids of the
cacsalpin-type from the roots of Caesalpinia pulcherrima, the structures of these
compounds vouacapen-5α-ol, 6β-cinnamoyl-7β-hydroxy-vouacapen- 5α-ol and
8,9,11,14− didehydrovouacapen-5α-ol, were elucidated through interpretation of
their spectral data. Sitostrol was also obtained.169

• Two Ellagitannins from the stem bark of Caesalpinia pulcherrima

Awasthi KK et al., 1997 isolated 2 ellagitannins from the stem bark of C.
Pulcherrima. These tannins have been assigned structures with glucose as the
carbohydrate core, esterified with two galloyl and one hexahydroxydiphenoyl
group and with a galloyl, a hexahydroxydiphenoyl and a m-digalloyl group,
respectively.170

• A New Furanoid Diterpene from Caesalpinia pulcherrima.

Ragasa CY et al., 2003 isolated a new cassane-type diterpeneisovouacapenol E
from the leaves of Caesalpinia pulcherrima, together with the known compounds
caesaldekarin A, spathulenol, caryophyllene oxide, phytol, and sitosterol.171

• Flavanoids from Caesalpinia pulcherrima

Srinivas et al., 2003 isolated two new 95 ulcherrim, 5,7-dimethoxy-30,40-
methylenedioxyflavanone and isobonducellin along with 20-hydroxy-2,3,40,60-
tetramethoxychalcone, 5,7-dimethoxyflavone and bonducellin from the aerial
parts of Caesalpinia pulcherrima.172

• Nutrient Contents of Pride of Barbados Seeds.

Yusuf AA et al., 2007 determined Physical parameters and nutrient contents of
the whole seeds and seed nuts of Caesalpinia pulcherrima L. Using gravimetric,
Spectrophotometric and titrimetric method of analysis. Organic matter was high,
followed by dry matter. Contained Crude proteins, carbohydrate, and crude
lipid. Abundance of mineral elements in whole seeds and seed nuts of C. Pulcherrima were found to be in the order: phosphorus > magnesium > sodium > potassium > calcium > iron. The calorie value was 217.47-312.15 kcal/100g.  

• Cassanediterpenoids from the stem of Caesalpinia pulcherrima

Pranithanchai et al., 2009 isolated cassanediterpenoids: 96 ulcherrima, pulcherrin B, pulcherrin C, neocaesalpin P, neocaesalpin Q and neocaesalpin R, from the stem of Caesalpinia pulcherrima.  

REPORTED PHARMACOLOGICAL ACTIVITIES:

• In vitro antiviral activities of Caesalpinia pulcherrima and its related flavonoids. Chiang LC et al., 2003 aimed to search for new antiviral agents from Chinese herbal medicine. Pure flavonoids and aqueous extract of C.P were used in experiments to test their influence on a series of viruses, namely herpes viruses (HSV-1, HSV-2) and adenoviruses (ADV-3, ADV-8, ADV-11). Results showed that extracts of C.P and its related quercetin possessed a broad-spectrum antiviral activity. Among them, the strongest activities against ADV-8 were fruit and seed, stem and leaf and flower, whereas quercetin possessed the strongest anti-ADV-3 activity. In conclusion, some compounds of C. Pulcherrima which possess antiviral activities may be derived from the flavonoid of quercetin. 

• Screening of Caesalpinia pulcherrima Linn Flowers for Gastric ulcer activity of leaves of Caesalpinia pulcherrima.

Anil k and Nirmala, 2004 studied the antiulcer activity of Petroleum ether extracts of Caesalpinia pulcherrima, in HCl/ethanol and aspirin and pylorus ligation models in rats. In aspirin and pylorus ligated model, the extract was
able to significantly reduce the ulcer score and increase in mucus content but had no effect on gastric juice volume or acid content.\textsuperscript{176}

- **Antimicrobial Activity of Leaf Extracts of Caesalpinia pulcherrima. Linn.**
  
  Chakraborthy GS and Kaushik KN, \textit{2009} evaluated the antibacterial and antifungal activities of Petroleum ether, chloroform, ethanol and water extracts of C.P using agar well diffusion method. Gentamicin 5\(\mu\)g/ml was used as standard. All the extracts showed antimicrobial activity. All the extracts exhibited in-vitro antibacterial activity. None of the extracts showed antifungal activity.\textsuperscript{177}

- **Antioxidant and cytotoxic activities of Caesalpinia pulcherrima.**
  
  Wood Pawar CR et al., \textit{2009} studied Antioxidant and cytotoxic activities of methanolic and aqueous extracts of C.P wood in \textit{in vitro} models. Both the extracts showed highly antioxidant activity, as evidenced by the low IC\textsubscript{50} values in both 1, 1- diphenyl-2-picryl hydrazyl (DPPH), nitric oxide and superoxide scavenging methods; the values were found to be less or comparable to those of gallic acid, the standard used. To determine the cytotoxic activity, extracts were tested for toxic effects to brine shrimp larvae. In this assay, the methanolic extract had little effect, but aqueous extract was relatively toxic. The antioxidant and cytotoxic activities may be attributed to the total phenolic content in the wood.\textsuperscript{178}

- **Development of Peacock flower extract as Anti-wrinkle formulation.**
  
  Soisuwan S et al., \textit{2010} evaluated antioxidant property of the ethanolic extract from the petals of C. Pulcherrima, and developed an anti-wrinkle product from the crude extract including the quality assessment. The results of DPPH
radical scavenging assay showed the strongest activity, followed by the extract of the orange petals and the yellow petals, respectively.

The ABTS cation radical scavenging assay demonstrated the strongest activity for the orange petals followed by the red petals and the yellow petals. Consequently, orange petals were chosen in order to develop an anti-wrinkle product in an O/W formula. The results demonstrated that the anti-wrinkle product had the efficacy of enhancing the elasticity of the skin. No irritation could be observed at the volunteer’s skin.\textsuperscript{179}

- **Analgesic and Anti-inflammatory**

  Activities Patel SS \textit{et al.}, 2010 determined analgesic and anti-inflammatory activities of methanolic extract of C.P flowers. Administration of methanolic extract exhibited significant analgesic activity in experimental animals using of acetic acid-induced writhing, tail immersion test and hot plate tests. Anti-inflammatory effect against carrageenan-induced paw edema in albino rats exhibited significant effect.\textsuperscript{180}

- **Anti-inflammatory and neuropharmacological activities of \textit{Caesalpinia pulcherrima} bark.**

  Utpal B \textit{et al.}, 2011 evaluated for anti-inflammatory and neuropharmacological activities of methanolic extracts of bark of C.P. Administration of extract (200 and 400 mg/kgP.o) showed a significant anti-inflammatory activity against carrageenan induced paw edema in rats. The extract of C.P barks also potentiated the pentobarbital induced sleeping time in mice, and decreased the open field score in open field test, decreased the number of hole crossed from one chamber in the hole cross test and decreased the head dip responses in hole board test.\textsuperscript{181}
• Evaluation of Anthelmintic activity of Caesalpinia pulcherrima bark against Pheretima Posthuma.

Satwadhar ND et al., 2012 evaluated crude extract of aqueous and hydroalcoholic Caesalpinia pulcherrima bark for anthelmintic activity (In vitro) on the Indian adult earthworms, which measured by paralysis and time of death of worm. Caesalpinia pulcherrima bark extracts showed a dose dependent inhibition of spontaneous motility of earthworms. Standard drug albendazole was used. Extract of aqueous and hydroalcoholic were found to be more potent than standard.
3.13 **BAUHINIA VARIEGATA LINN.**

**Botanical name**: *Bauhinia variegata*

**Synonym**: *Phanera variegata* (L) Benth

**Family**: *Caesalpiniaeae*

**Description:**

*Bauhinia variegata* Linn. Is a medium-sized, deciduous tree, found throughout India, ascending to an altitude up to 1800 m in the Himalayas. It was named Bauhinia after the Bauhin brothers who were sixteenth century herbalists\(^{183}\).

The plant is known by various names in different languages as under.

<table>
<thead>
<tr>
<th>Language</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>Mountain Ebony</td>
</tr>
<tr>
<td>Kannada</td>
<td>Kempu mandara</td>
</tr>
<tr>
<td>Marathi</td>
<td>Rakta kanchan</td>
</tr>
<tr>
<td>Hindi</td>
<td>Kachnar</td>
</tr>
<tr>
<td>Tamil</td>
<td>Shemmandarai</td>
</tr>
<tr>
<td>Telugu</td>
<td>Devakanchanamu</td>
</tr>
<tr>
<td>Malyalam</td>
<td>Chuvanna – mandaram</td>
</tr>
</tbody>
</table>

**Morphology:**

Bark is grey with longitudinal cracks, pale pink inside. *Bauhinia variegata* Leaves are rather wide than deep, 10-15 cm long, pubescent beneath when young, rigidly subcoriaceous, deeply cordate with two leaflets, connate for about two-thirds up, leaflets are ovate, rounded at apex.

Flowers are variously coloured, the uppermost petal darker and variegated, usually looking before the leaves in short axillary or terminal racemes lateral, sessile or short peduncled corymbs, , stamens 5, staminodes are absent, fruits flat; 10-15 seeded, hard glabrous dehiscent pods.
**Plate No.6** *Bauhinia variegata* Linn.

**Plate No.7** Barks of *Bauhinia variegata*

**Plate No.8** Leaves and Flower of *Bauhinia variegata* Linn.

**Plate No.9** Root of *Bauhinia variegata* Linn.
FOLKLORE/TRADITIONAL USES

*Bauhinia variegata* Linn. is widely used in folklore medicine. Its bark, root, leaves, seeds and flowers are used for their medicinal properties. It has been used in dyspepsia, bronchitis, leprosy, ulcer, to prevent obesity, as an astringent, tonic, etc. *Bauhinia variegata* Linn. is widely used in Ayurveda as a tonic to the liver and even the same is reported in folklore medicine.

Root of *Bauhinia variegata* Linn. is not taken up much for pharmacological properties. Instead of root of *Bauhinia variegata*, barks has anthelmintic, astringent properties and also have been used as tonic. It has been also used in ulcer, leprosy, tuberculosis and skin ailments. Bark decoction is used in condition of dysentery. Its decoction is also taken up to give tone and vitality to body.

The *Bauhinia variegata* leaves contain vitamin C (146 mg %). They are rich source in reducing sugars in diabetes and have very good nutritive value. The leaves infusion is used for cure of diarrhoea, dysentery and piles.

The dried buds of *Bauhinia variegata* are used for the treatment of worms, piles, diarrhoea, dysentery, wound and tumours.

- The bark of *Bauhinia variegata* (BV) has been traditionally used and also reported in the Ayurvedic classics, to have antidiabetic property.
- A decoction of the buds is given in cough, piles, haematuria and menorrhagia. The flowers are laxative. Flower buds are pickled.
- An aqueous extract of the plant was found to be effective in induced goiter in rats.
- A gargle made from the bark with the addition of extracts of acacia pods and pomegranate flowers is a remedy.
- In treating salivation and sore throat.
• Bark rubbed into an emulsion with rice water and administered with the addition of ginger in scrofulous enlargement of the glands of the neck. A paste made of the bark together with dried ginger is also applied to scrofulous tumours.

• This plant is used in malaria and is also an antidote to snake poison.

REPORTED CONSTITUENTS OF BAUHINIA VARIEGATA LINN:

- The stem contains sitosterol, lupeol, kaempferol-3-glucoside and 5,7-dihydroxy and 5,7-dimethoxy flavanone-4-O-L-rhamnopyranosyl-D-glucopyranosides.

- The pale violet flowers contain cyanidine-3-glucoside, malvidin-3-glucoside, malvidin-3-diglucoside, and peonidin 3-diglucoside.

- While the white flowers contain kaempferol-3-galactoside and kaempferol-3-rhamnoglucoside.

- These five flavonoids quercetin, rutin, apigenin and apigenin 7-O-glucoside have been isolated from the different parts of Bauhinia variegata has benn identified as.

- Phytochemical analysis of the root bark of Bauhinia variegata Linn was reported to contain a new flavanone: (2S)-5,7-dimethoxy-3′-4′-methylene dioxyflavanone (1) and a new dihydrobenzoxepin 5,6-dihydro-1,7dihydroxy-3,4-dimethoxy-2-methylidibenz (b,f) oxepin.

REPORTED PHARMACOLOGICAL ACTIVITY

- Antimicrobial activity & antifungal activity- Sharma R.N. et al., (1996) evaluated that methanolic extracts of leaves of Bauhinia variegata shown
antimicrobial activity & antifungal activity was shown against *Aspergillus fumogalus, Aspergillus niger*.

- **Antitumor activity- Rajkapoor B et al (2003)** Antitumor activity of ethanol extract of *Bauhinia variegata* was evaluated against Dalton’s Ascitic lymphoma in Swiss albino mice. A significant enhancement of survival time of BVE treated tumor bearing mice was found with respect to control group. BVE was able to reverse changes in haematological parameters protein and PCV consequent to tumor inoculation.

- **Anti-inflammatory activity- Yadava RN, et al (2003)** Anti-inflammatory activity of a novel flavanol glycoside from *Bauhinia variegata* Linn. Isolation and structural elucidation of a novel flavanol glycoside 5,7,3′,4′-tetrahydroxy-3-methoxy-7-O-alpha-L-rhamnopyranosyl (1->3)-O –galactopyranosi-de from the roots of *Bauhinia variegata* and its structure was identified by spectral analysis and chemical degradations. The novel compound showed anti-inflammatory activity.

- **Cytoprotective- Rajkapoor B. Et al., (2003)** studied chemoprevention and cytotoxic effect of *Bauhinia variegata* against N-nitrosodiethylamine induced liver tumors and human cancer cell lines. They found that oral administration of ethanol extract of *Bauhinia variegata* effectively suppressed liver tumor as revealed by decrease in levels of serum glutamate pyruvate transaminase, serum glutamate oxaloacetate transaminase, alkaline 104 olyherbal 104, total bilirubin, gamma glutamate transpeptidase, lipid 104 olyherbal, glutathione 104 olyherbal and glutathione S-transferase. The extract produced an increase in enzymatic antioxidant (superoxide dismutase and catalase) levels and total proteins when compared to those in liver tumor bearing rats. The
Histopathological changes of liver samples were compared with respective controls. Plant extract was found to be cytotoxic against human epithelial larynx cancer and human breast cancer cells\textsuperscript{189}.

- **Hepatoprotective activity- Bodakhe SH et al (2007)** were studied hepatoprotective properties of *Bauhinia variegata* bark Extract\textsuperscript{190}.

- **Proteinase inhibitors- Oliva MLV et al (2009)** Inhibitors isolated from different species of Bauhinia seeds inhibit blood clotting enzymes, as well as other serine and cysteine proteinases. Two varieties *B. Variegata* seeds, shown to possess Plant Kunitz type inhibitors – *B. Variegata* trypsin inhibitors, viz. *Bauhinia variegata Candida* trypsin inhibitor (Bvc TI) and *B. Variegata lilac* trypsin inhibitor (BvlTI) are proteins, about 20,000, with four cysteine residues forming two disulphide bridges in one polypeptide chain\textsuperscript{191}.

- **Anticarcinogenic & Antimutagenic- Agarwal RC et al (2009)** Anticarcinogenic and antimutagenic potential of *B. Variegata* extract was evaluated in Swiss albino mice using a skin carcinogenesis and melanoma tumour model, along with micronucleus and chromosomal aberration tests. In the skin papilloma model, significant prevention, with delayed appearance and reduction in the cumulative no. of papillomas was observed in the DMBA + Kachanar + croton oil treated group as compared to the DMBA + Croton Oil group. C57 BI mice which received a 50 % methanolic extract of Kachanar extract at the doses of 500 and 1,000 mg/kg body weight for 30 days showed increase in life span and tumour size was significantly reduced as compared to controls. In antimutagenicity studies, a single application of Kachanar extract at doses of 300, 600 and 900 mg/kg dry weight, 24 hours prior the i.p. administration of cyclophosphamide (at 50 mg/kg) significantly prevented
micronucleus formation and chromosomal aberrations in bone marrow cells of mice, in a dose dependent manner\textsuperscript{192}.


- **Antioxidant and antihyperlipidemic – Rajani GP et al., (2009)** Ethanolic and aqueous extract of root of *Bauhinia variegata* has been studied for antioxidant and antihyperlipidemic activities\textsuperscript{194}.

- **Immunomodulatory activity- Patil J. K. Et al., (2010)** studied the in-vitro immunomodulatory activity of *Bauhinia variegata* Linn (Caesalpiniaceae) stem bark extracts n human neutrophils. The acetone-water, aqueous extracts and isolated compound (tannin) were screened for their possible Immunomodulatory activity by assessing nitroblue tetrazolium test, phagocytosis of killed *Candida Albicans*, candidacidal assay, neutrophil locomotion and chemotaxis. The acetone:water and isolated compound of *Bauhinia variegata* Linn stem bark showed predominantly significant activity on *in-vitro* human neutrophils in all parameters, which are comparable to standard and control\textsuperscript{195}.

- **Insulin Release Enhancer- Frankish N et al (2010)** The presence of insulin-like molecule was recently demonstrated in the leaves, where a ‘chloroplast protein’ was found that has a partial amino acid sequence identical to that of Bovine insulin. This protein may be responsible for the lowering of blood glucose concentration when it is injected in alloxan induced diabetic mice. A major metabolite of the ethanolic extract of leaves; roseoside, demonstrates
insulinotropic activity toward pancreatic β-cells of the INS-1 cell line and may act in conjunction with the chloroplast protein to contribute to the overall antidiabetic properties\textsuperscript{196}.

- **Antioxidant and nephroprotective activity- Sharma R. K. (2011)** studied effect of ethanolic and aqueous extracts of *Bauhinia variegata* Linn. On Gentamicin-induced nephrotoxicity in rats. The antioxidant activity of both ethanolic and aqueous extracts of root of *Bauhinia variegata* Linn. Was carried out by in-vitro models such as scavenging of free radicals like 1,2-diphenyl1-2-picrylhydrazyl (DPPH), nitric oxide and superoxide. Both ethanolic and aqueous root extracts of *Bauhinia variegata* Linn. Produced significant free radical scavenging activity. Both the extracts produced significant nephroprotective activity in Gentamicin induced nephrotoxicity model as evident by decrease in elevated serum creatinine, serum urea, urine creatinine and BUN levels, which was further confirmed by histopathological study\textsuperscript{197}.

- **Analgesic and Anti-Ulcer- Yamini R et al.(2011)** The analgesic activity was evaluated by acetic acid induced writhing and hot plate models. Pylorus ligation, ethanol and aspirin induced ulcer models were employed for evaluating antiulcer activity Both aqueous and ethanolic extracts of root of *Bauhinia variegata* Linn. At both the doses produced significant analgesic activity when evaluated by hot plate model. BVA 200, BVE 200 and 400 produced significant analgesic activity evaluated through acetic acid induced writhing model when compared to standard drug Indomethacin. BVA and BVE at both the doses exhibited good anti ulcer activity in all the three ulcer models\textsuperscript{198}.
• **Antipyretic activity** – Mandal S et al (2011)- A comparative antipyretic activity of the crude extracts of the ariel parts of Glycosmis pentaphylla and Bauhinia variegata\(^{199}\).

• **Nephroprotective activity**- Saumya R. P. Et al., (2011) evaluated nephroprotective effect of *Bauhinia variegata* (Linn.) whole stem ethanolic extract against cisplatin-induced nephropathy in rats. Acute nephrotoxicity was induced by i.p. injection of cisplatin. Ethanol extract at 400 mg/kg decreased the serum level of creatinine and urea associated with a significant increase in body weight and urine volume output as compared to the toxic control group. The ethanol extract of B. Variegata at 400 mg/kg (b.w.) exhibited significant and comparable nephroprotective potential to that of the standard 108olyherbal drug cystone\(^{200}\).
3.14 CAESALPINIA CRISTA LINN.

Botanical name : *Caesalpinia crista* Linn.

Synonym : Putika, Kantaki, Lata Karanja, Gray nicker, *Caesalpini bonducella*

Family : *Caesalpiniaceae*

**Description of Plant:**

*Caesalpinia crista* belonging to Family: *Caesalpiniaceae*. Found throughout India and tropical countries of the World. Pütika or Atika terms are found in the vedic literature. It is an effective remedy for acute pain abdomen (anti-spasmodic), malarial fever.

The plant was much confused with *Caesalpinia bonducella* (Syn. C. bonduc). Beside this species like *C. nuga* and *C. jayoba* are also sometimes wrongly designated as synonyms for *C. crista*. “Bonducella” the name of the species is derived from the Arabic word “Bonduce” meaning a “little ball” which indicated the globular shape of the seed.\(^{201-202}\)

The plant is known by various names in different languages as under.

- **English** : Fever nut
- **Kannada** : Gajaga kaya
- **Bangali** : Natakani
- **Hindi** : Kantakareja
- **Tamil** : Kalichikai
- **Telugu** : Gachakaya
- **Marathi** : Sagargota
Plate No.10 Caesalpinia crista Linn

Plate No.11 Seed of Caesalpinia crista Linn

Plate No.12 Leaves and Flowers of Caesalpinia crista Linn.

Plate No.13 Fruits of Caesalpinia crista Linn.
Macroscopic Characteristics

Leaves: Leaves are with large, leafy, branched, basal appendages; 30-60 cm.

Seeds: Seeds are hot and dry, globose or rounded. Seed coat is hard, glossy, and greenish to ash grey in color.

It is traversed by circular and vertical faint markings of the cracks, forming uniform rectangular to squarish rectulations all over the surface. Seeds 1.2, oblong, lead-colored, 1.3 cm. long.

Flowers: Flowers in dense (usually) long-peduncled terminal and supraaxillary racemes dense at the top, lax downward, 15-25 cm. long; pedicels very short in bud, elongating to 5 mm. in flower and 8 mm in fruits.

REPORTED CONSTITUENTS OF CAESALPINIA CRISTA LINN:

There are various active constituents of the plant found in different part of the plant like stem, fruit, seeds, flowers which shows the immense potential activity.

The seeds contain fatty oil which contains glycerides of some acids eg. Palmitic acid, stearic acid, and two phytosterols and other sitosterol.

Previous chemical studies on Caesalpinia crista have resulted in the isolation of cassane furanoditerpenes and flavonoids.

Recent study has isolated two new homo isoflavonoids, caesalpinianone and 6-O-methylcaesalpinianone along with natural products, namely, hematoxylol, stereochelon A, 60-O-acetylloganic acid, 40-O-acetylloganic acid, and 2-O-b-D-glucosyloxy-4-methoxybenzenepropanoic acid.

The herb Caesalpinia Crista contains the many diterpenoids from their different part specially from the stem and root. With previously invented cassane butenolide hemiketals, four other cassane diterpenes is isolated. They are the...
caesalpinolide-C, caesalpinolide-D, caesalpinolide-E and cassane furanoditerpene along with other known compounds.\textsuperscript{206,207}

From the stem and roots of \textit{Caesalpinia crista} isolated the nine new cassane-type diterpenes, named taepeenin A–I, and two new norcassane-type diterpenes, named nortaepenin A–B, were isolated from the along with three known diterpenes: vinhaticoic acid, methyl vinhaticoate and ent-11b-hydroxy-rosa-5,15-diene.

Recently four flavonoids compound have been isolated from the flower of caesalpinia crista 3,5,7,3’,4’ pentahydroxy flavones-3-O-β-D-Xylopyronosyl-7-O-α-L-arabinopyranosyl-(1→3)-O-α-L-rhamnopyranoside (A), 4’-hydroxy 5,7-dimethoxy flavones 4-O-β-D-xylopyranosyl-(1→3)-O-β-D-glucopyranosyl-(1→4)-O-α-L-rhamnopyroside (B), 5-2’-dihydroxy-6,7-dimethoxy isoflavone (C), and 3-5-7,3’,4’,5’-hexahydroxy flavones (D) by various colour reaction, chemical degradation, and spectral analysis.\textsuperscript{208}

\section*{REPORTED PHARMACOLOGICAL ACTIVITY:}

\subsection*{Adaptogenic activity}

\textbf{Kannur DM, et al., (2006)} Adaptogenic activity of \textit{Caesalpinia bonduc} seed extracts in rats was reported by using cold stress model and swim endurance model. It showed that the extracts significantly increased the swim endurance time. Stress induced animals exhibited hypoglycaemia as well as depletion in serum cortisol level and increased total leukocyte count, the extracts showed a significant action in overcoming these imbalances.\textsuperscript{209}

\subsection*{Anthelmintic activity}

\textbf{Ganesh HW, et al., (2010)} In the in vitro study methanolic and aqueous extracts of leaves of \textit{Caesalpinia bonduc} Linn. Flem were investigated for their anthelmintic
activity against Pheretima posthuma and Ascardia galli. The alcoholic extract of *Caesalpinia bonducella* was evaluated for the anthelmintis activity against the earthworm Pheretima posthuma. Both the extracts showed significant anthelmintic activity.\(^{210}\)

In previous paper drug but this study was for the polyherbal preparation. Anthelmintic activity of *Chenopodium album* and *Caesalpinia crista* were determined against the trichostrongylid nematodes of sheep. These data shows both *Caesalpinia crista* and *Chenopodium album* possess anthelmintic activity in vitro and in vivo.\(^{211}\)

**Anti-inflammatory activity**

**Shantanu K, et al., (2010)** In this study wistar rats of either sex were treated with petroleum ether extract of *Caesalpinia bonduc*. Inflammation was induced in rat paw by injecting 0.1 ml of carrageenan. The extract significantly decreased the inflammation at dose level of 100 mg/kg. The anti-inflammatory activity of petroleum ether extract of *C. bonduc* was considered may be due to action of phytosterol.\(^{212}\)

**Anti-inflammatory, antipyretic and analgesic activities**

**Shukla S, et al., (2010)** Varied concentrations of the seed oil of *C. bonducella* (100, 200 and 400 mg/kg orally) were tested in carrageenan induced rat paw oedema, brewer's yeast-induced pyrexia, acetic acid-induced writhing and hot plate reaction time in experimental rats. The paw volumes, pyrexia and writhes in experimental rats were reduced significantly (\(p < 0.05\)) as compared to that of control, and hot plate test showed significant licking effect in rats.\(^{213}\)

**Anti-amyloidogenic**

**Rao KSJ, t al., (2010)** It is evidenced that *Caesalpinia crista* leaf aqueous extract has anti-amyloidogenic potential. The studies on pharmacological properties of *C. crista* are very limited.
As amyloid beta (Aβ) is the major etiological factor implicated in Alzheimer’s disease (AD), the recent studies aimed to decrease Aβ levels or prevention of Aβ aggregation which are the major targets for therapeutic intervention. Thioflavin-T assay and transmission electron microscopy (TEM) were used for monitoring of aggregation.

Antibacterial activity

The methanol extract and four triterpenoids isolated from the seeds of *Caesalpinia bonducella* showed a wide range of inhibiting activity against both gram-positive and gram-negative bacteria.

**Antimicrobial activity**

*Rajesh D, et al., (2009)* The in vitro antimicrobial activities of seed coat and seed kernel extracts were investigated by microbroth dilution assay. In vitro activities of hydroalcoholic extracts were investigated in rat models of chronic pseudomonas aeruginosa, pneumonia.

**Antidiabetic activity**

*Kannur DM, et al., (2006)* The seed extracts of *Caesalpinia bonducella* were used for determining the antidiabetic activity in wistar rats in case of alloxan induced hyperglycemia. After the oral administration of the extracts (300 mg/kg), significant antihyperglycemic action as well as it lowered the BUN levels significantly was observed. In the same study the action of the extracts on diabetes induced hyperlipidemia was analyzed where the extracts significantly lowered the elevated cholesterol as well as LDL level.

**Antifilarial activity**

*Rastogi S, et al., (2008)* This study was assessed to the antifilarial activity of *caesalpinia bonducella* seed kernel against rodent filarial parasite in experimental
model. Microfilaricidal, macrofilaricidal and female worm sterilizing efficacy were evaluated.

**Antioxidant activity**

**Shukla S, et al (2009)** The study was aimed to evaluated the in vitro potential of ethanolic extract of *Caesalpinia bonducella* seeds as a natural antioxidant. The extract inhibited the hydroxyl radical, nitric oxide, superoxide anions. Antioxidant activity, scavenging activities for various ROS, iron chelating activity and phenolic and flavonoid contents was evaluated.

**Hepatoprotective activity**

**Kumar RS, et al., (2010)** The study was carried out to determine the hepatoprotective and antioxidant effect of methanol extract of *Caesalpinia bonducella* in Wistar albino rats. The injury were induced with carbon tetrachloride in liquid paraffin 3 doses (i.p.) at 72 h interval.

**Nootropic Activity**

*Caesalpinia crista* seed kernels extract was assessed for learning and memory enhancer. In mice, amnesic effect of scopolamine was ameliorated using aqueous extract of dried seed kernels of *Caesalpinia crista*. Using morris water maze paradigm as the exteroceptive behavioral method, aqueous extract of dried seed kernels of *Caesalpinia crista* linn. is compared to standard drug (piracetam) in scopolamine induced amnesia in mice.

**Immunomodulatory activity**

The evaluation of immunomodulatory potential by oral administration of ethanolic seed extract of *Caesalpinia bonducella* (200–500mg/kg) evoked a significant increase in percent neutrophil adhesion to nylon fibers. Neutrophil adhesion test, haemagglutinating antibody (HA) titre, delayed type hypersensitivity (DTH) response,
phagocytic activity and cyclophosphamide induced myelosuppression were determined by in vivo experiments.\textsuperscript{222, 223}

**Contractile activity**

Contractile activity was studied in isolated pregnant rat myometrium preparations of uterus. The increased contractile force by leaf extract of *caesalpinia bonduc* was compared with acetylcholine obtained contraction. It is reported that contractile effect which may be due to an activation of the cholinergic mechanism.\textsuperscript{224}

**Antifeedant activity**

*Caesalpinia crista* seed extracts were investigated in the laboratory against *Helicoverpa armigera* (Hubner). The extracts exhibited powerful antifeedant and growth disruption activity. Among the different extract of *Caesalpinia crista*, maximum antifeedance is caused by methanolic extract, followed by hexane extract, ethyl acetate extract, butanol extract and aqueous extract.\textsuperscript{225}