INTRODUCTION
**1.0 INTRODUCTION**

Medicinal plants and plant derived products play an important role in the alleviation sufferings of human beings. Plant medicines are the most widely used medicines in the world today. 85% of the world's population employs herbs as their primary medicines. Billion of people worldwide, use natural plant-based remedies for both acute and chronic health problems, from treating common colds to controlling blood pressure and cholesterol. Since ancient times literature is available on the use of medicinal plants in the treatment of various diseases. Many documentary records are available for showing the role of medicinal plants and plant derived products. The beneficial role of plant derived products in therapeutic treatment is an important breakthrough in the history of mankind. Since ancient time medicinal plants have proved their efficacy and safety in the therapeutic treatment of diseases. The evidences for the therapeutic actions of herbal drugs are documented in Ayurvedic, Chinese, European and African system of medicine [1].

Ayurveda is an ancient Indian system of medicine. Ayurveda is in therapeutic practice since last thousands of years. Ayurveda provides information about various diseases, their symptoms and specific natural remedy for curing the diseases.

There is an increasing interest in and support for the search of new and useful drugs from higher plants in countries such as India, China, Japan, and the Federal Republic of Germany and amongst many nations all over the world. 50% of the estimated 2,50,000 plant species found on earth come from tropical forests. The number of higher plant species (angiosperms and gymnosperms) on this planet is estimated at 2,50,000, with a lower level at 2,15,000 and an upper level as high as 5,00,000. Of these, only about 6% have been screened for biologic activity, and a reported 15% have been evaluated phytochemically.

India is the largest producer of medicinal herbs. India has 15,000-18,000 species of flowering plants, 2,500 algae, 23,000 fungi and 1,600 types of microorganisms. This figure has shown a vast and tremendous biodiversity potential in India, which can be utilized in many sectors [2].

Of this about 15,000 to 20,000 plants have good medicinal value. However only about 7,500 plants have been used for their medicinal values. The above figure themselves explain huge and tremendous hidden potential lying in the plants. A lot of plants are yet to be explored for their medicinal values.
1.1 PLANTS USED IN MEDICINE

The plants can serve as sources of futuristic drugs, which can be used to alleviate or treat many kind of diseases [3]. Plant medicines are far and away safer, gentler and better for human health than synthetic drugs. In the last few decades naturally, pharmaceutical companies have given keen stress on research and development of namely occurring plant and plant derived drugs. The modern approach involves isolation, characterization and pharmacological studies of plants with the help of sophisticated instruments. The outcome of such research work was the generation of new drugs, which are found to be active in the specific diseases [4]. Natural Products has become an integral part of human health care system. The popularity of these products is due to its less toxicity and efficacy. Most of the world population depends on the traditional medicine. World Health Organization (W. H. O.) has formulated remedies of traditional medicine to study their potential usefulness, safety and efficacy [5]. The global herbal product market is worth US$ 14.2 billion and is growing at a rate of about 9-15% annually. The annual turnover of the Indian herbal medicinal industry is about Rs.2,300 crores as against the pharmaceutical industry’s turnover of Rs.14,500 crores with a growth rate of 15% [6].

1.2 CARDIAC DISEASES

Cardiovascular disease is a wide-encompassing category that includes all conditions that affect the heart and the blood vessels. Cardiovascular disease is the number one cause of death all over the globe. Many risk factors are associated with
Chapter 1 Introduction

cardiovascular disease; most can be managed, but some cannot. The aging process and hereditary predisposition are risk factors that cannot be altered. Until age 50, men are at greater risk than women of developing heart disease, though once a woman enters menopause, her risk triples.

Many people with cardiovascular disease have elevated or high cholesterol levels. Low HDL cholesterol (known as the "good" cholesterol) and high LDL cholesterol (known as the "bad" cholesterol) are more specifically linked to cardiovascular disease than is total cholesterol. A blood test, administered by most healthcare professionals, is used to determine cholesterol levels.

Atherosclerosis (hardening of the arteries) of the vessels that supply the heart with blood is the most common cause of heart attacks. Atherosclerosis and high cholesterol usually occur together, though cholesterol levels can change quickly and atherosclerosis generally takes decades to develop.

The link between high triglyceride levels and heart disease is not as well established as the link between high cholesterol and heart disease. According to some studies, a high triglyceride level is an independent risk factor for heart disease in some people. High homocysteine levels have been identified as an independent risk factor for heart disease. Homocysteine can be measured by a blood test that must be ordered by a healthcare professional.

Hypertension (high blood pressure) is a major risk factor for cardiovascular disease, and the risk increases as blood pressure rises. Glucose intolerance and diabetes constitute separate risk factors for heart disease. Smoking increases the risk of heart disease caused by hypertension. Abdominal fat, or a "beer belly," versus fat that accumulates on the hips, is associated with increased risk of cardiovascular disease and heart attack. Overweight individuals are more likely to have additional risk factors related to heart disease, specifically hypertension, high blood sugar levels, high cholesterol, high triglycerides, and diabetes. People may experience symptoms as difficulty in breathing during exertion or when lying down, fatigue, lightheadedness, dizziness, fainting, depression, memory problems, confusion, frequent waking during sleep, chest pain, an awareness of the heartbeat, sensations of fluttering or pounding in the chest, swelling around the ankles, or a large abdomen.

Worlds health organization (W.H.O.) predicts that, 'India will have 100 million or 60% of the world heart patients by 2010.' This figure put forth a challenge of new millennium in front of us. In India heart diseases are not related to a particular class of people they have been spread at all the segments of society. Change in life style, high stress level, high fat diet, diabetics, high serum lipid levels, job insecurity, genetic problems, modernization, increased environmental pollution are some of the causes of heart diseases. According to the cardiological society of India, 50 million of people in India suffer from heart diseases, this figure warns about the seriousness of the diseases.

Heart diseases have spreaded all over the world. In the developing countries major portion of their budget is spent on the health care system. Due to the serious nature
of heart diseases it is very essential and urgent to fight against these diseases in a systematic manner. The union of ancient knowledge and modern technologies will definitely help us to fight against these diseases successfully.

1.3 AYURVEDA IN HEART DISEASE

Ayurveda predates Bible it is believed to be between 3,000 and 5,000 years old, originating in India's Vedic period, and is reportedly the basis of Tibetan, Buddhist, Taoist and Greek medicine. "Ayurveda" comes from the words ayur (life) and veda (knowledge), which together translate into "the science of life."

It is part of the Atharva Veda, one of the four spiritual books known as the Vedas written by Srila Vyasadeva (also referred to as Vyasa) in the ancient language of Sanskrit. Ayurveda later became an Upaveda (a branch of the Veda) because it dealt more with healing than spirituality.

Historians credit three treatises as the foundation behind the practice of Ayurveda being used today. The Charaka Samhita was written sometime around 1000 B.C. and states the beginning of illness comes from a loss of faith in the Divine. The Sushruta Samhita, which is an overview of internal medicine, discusses eight branches in Ayurveda: general medicine, surgery, eye diseases, toxicology, psychiatry, pediatrics, gynecology, and virility and fertility. The third, Ashtangha Hridaya Samhita, is a combination of the other two treatises. The physicians and surgeons practicing Ayurveda in ancient times were considered holy people and believed health and spirituality are intertwined. Reportedly, the first Ayurvedic practitioners received their training via meditation and divine intervention.

The concept of Ayurveda is based on a combined study of body (sharira), sense organs (indriyas), mind (manas) and soul (atman) [7]. Equilibrium of all these is related to health and their disturbance is related with diseases. Homeo-stasis of the internal milcu (dhatusamaya), or equilibrium of the various dhatus, is considered essential for absence of disease. When an imbalance exists among any of the three doshas, an Ayurveda suggests a unique combination of foods, exercise, meditation and herbs to bring the doshas back into normal. Using Ayurvedic herbs stimulates the function of specific organs in the body, possibly by altering hormones, affecting immunity and neurotransmitters, and conveying antioxidant properties[8]. The exact origin of Ayurveda cannot be dated precisely, but the original text is believed to have been written in ten million verses in one thousand chapters. The knowledge of Ayurveda then gradually descended through several sages, including Bharadwaja, Aitreya, Agnivastha, and finally Charaka and his students who compiled the text known as ‘Charaka Samhita’ which dates between 600 and 1000 B.C.

Cardiovascular problems have been dealt in detail in Ayurveda, which describes 'Hridaya' (heart) as a body organ governing emotions and circulating blood to keep a person alive and healthy. 'Heart Disease' (Hrudroga) is a global phenomenon. It is now becoming a major health problem even in the developing countries [4]. The
predisposing factors are heredity, high blood pressure, diabetes, high serum cholesterol and smoking. The way of living and the way of feeling appear to be quite an important factor in its increasing incidence [9]. Cardiac problems arise mainly due to improper diet and stressful life styles, which lead to thickening of arteries (dhamani praticaya) or hardening of arteries (dhamani kathinaya) resulting in angio-obstruction (vata dosa) and angina (ruja). Heart diseases are badly affecting millions of people worldwide. Ayurveda has proved to be very useful in treatment of heart diseases. Ayurveda has given different plants and formulations, which are useful in managing heart diseases [10-11].

Ayurveda suggest following things to avoid heart diseases:

- Coffee and Cigarette smoking
- Regular exercise helps to eliminate body fat, lower total cholesterol and raise HDL cholesterol that prevents fatty - cholesterol deposits. According to Ayurveda exercise improves the body, depletes excess fats, brings lightness of the body.
- Live life positively with spiritual practice.
- Eating a primarily vegetarian diet consisting of fresh fruits and vegetables, whole grains and legumes, and non-fat organic dairy products will provide protection for heart.
- Avoid Ama creating foods, oily foods. For a healthy heart diet, eat less meat, cheese, restaurant and packaged foods.
- Spices can often have a very powerful and specific effect on a tissue or dhatu. Fenugreek is very strong in its influence on meda - fat, carbohydrate metabolism and hormones. Since many heart problems are caused by excess meda it is an important spice for heart health. Almost all the Ayurvedic preparations that deal with fat metabolism, sugar metabolism and diabetes have fenugreek as a component.

Ayurveda has given valuable information for the treatment of heart diseases. The different types of heart disorders and their remedy as per ayurveda has been described as:

1.4 TREATMENT OF CARDIAC DISEASES

Angina

It is characterized by pain that is crushing, constricting, strangling, suffocating, sharp, or burning. It is normally felt in the chest but may also occur in the peripheral areas such as the jaw or abdomen. Pain that occurs with exertion and recedes with
rest. When too little blood reaches the heart, the condition is called ischemia. Chest pain, or angina, may occur. The pain can vary in occurrence. It may be mild and intermittent, or it may be more pronounced and steady. It can be severe enough to make normal everyday activities difficult. However, in some cases, it may cause no symptoms (a condition called silent ischemia). If a blood clot suddenly cuts off most or all blood supply to the heart, a heart attack results [12-14].

**Symptoms:** Weakness, sweating, shortness of breath, anxiety, palpitations, nausea, light-headedness.

**Treatment:** An Ayurvedic mixture of herbs and minerals known as Abana formulation found to be significantly reduce the frequency and severity of angina attacks.

i. Ayurvedic herb Guggul is shown to reduce the serum cholesterol levels.

ii. Green Tea is helpful to keep cholesterol from clogging arteries.

iii. Garlic use prevent the oxidation of LDL cholesterol, may prevent the liver from producing excess fat and cholesterol.

iv. Hawthorn has been indicated for dilating coronary blood vessels, to improve the flow of blood to the heart. It also strengthens the heart muscle and works to help the body rid itself of excess salt and water.

v. Turmeric helps to lower blood cholesterol levels by stimulating the production of bile. It also prevents the formation of dangerous blood clots that can lead to heart attack.

vi. Ginkgo biloba is helpful to improve the flow of blood throughout the body. It is also an antioxidant.

vii. Alfalfa leaves and sprouts help to reduce the blood cholesterol levels and plaque deposits on artery walls.

viii. Citrin - an extract from the plant *Garcinia cambogia*, inhibits the synthesis of fatty acids in the liver.

Other herbs that are beneficial for cardiovascular disorders include barberry, black cohosh, butcher's broom, cayenne (capsicum), dandelion, ginseng, and valerian root.

**Hypertension (High Blood Pressure)**

Blood pressure is the force of blood against the walls of arteries [15]. Blood pressure has two components—the systolic pressure (It is the force that blood exerts on the artery walls when the heart is pumping) over the diastolic pressure (it is the residual force that remains when the heart relaxes between beats). Elevated in blood pressure, it raises risk for heart attack and stroke. Low blood pressure is related to weakness of the digestive fire. It is most common in Vata types, due to poor circulation. In Kapha
it occurs because of congestion and stagnation, with phlegm clogging and reducing the blood flow. In Pitta it is mainly associated with anemia or damaged liver function.

**Types of Hypertension** [16]: From Ayurvedic perspective, hypertension is commonly a Pitta condition. However, it can occur in the other doshas as well.

**Vata Hypertension:** Symptoms: The blood pressure may rise suddenly and fall suddenly with nervous tension. Irregular pulse both in rhythm and strength, an increase in blood pressure will be followed by worry, strain, overwork, anxiety or insomnia, frequently associated with nervous system disorders.

**Kapha Hypertension:** Symptoms: The blood pressure remains continually high. (no fluctuation as in Pitta hypertension.), obesity, tiredness, edema, high cholesterol.

**Pitta Hypertension:** Symptoms: flushed face, red eyes, violent headaches, sensitivity to light, nosebleeds, anger, irritability, burning sensations, wiry and tight pulse, associated with liver disorders and the accumulation of internal heat.

**Treatment** [17]

Use of dairy, butter, eggs and high fat foods should be avoided. Mustard and onions should be included in diet.

i. Crushed clove (with honey) once or twice a week found to be useful.

ii. Nutmeg or Saraswat powder is prescribed in warm milk.

iii. Ashwagandha preparations [18]: Ashwagandha - 1 part, Valerian - 1 part,

Gotu kola - 1 part – helps to calm the nerves and relieves heat and stress. Preparation should be mixed well and 1-3 grams should be taken with warm water or with ghee.

iv. Arjuna preparations like Trikatu are very useful.

v. Herbs: Herbs such as gotu kola [19], calamus, valerian, skullcap, jatamansi, turmeric, cinnamon, ginger, cayenne, garlic, black pepper myrrh, motherwort, hawthorn berries, barberry, katuka and cardamom are recommended herbs for this condition. For Vata types garlic is used.

vi. For Kapha types cayenne or Trikatu is used.

vii. For Pitta types, saffron or turmeric in a base of aloe gel is used.

viii. Gotu kola is another useful herb for Pitta hypertension.

ix. Brahma Rasayana and Saraswat powder have also been used.

**Heart Attack (Myocardial Infarction)**

A heart attack (myocardial infarction) occurs when a coronary artery abruptly fails to deliver blood to a part of heart. Coronary arteries are the blood vessels on the surface
of heart. They bring oxygen and nutrients to heart muscle (myocardium). Sometimes fat, circulating cholesterol and other substances combine to form a hard substance known as plaque. The plaques also attract blood components, which stick to the artery wall lining. The build up of plaque may clog the arteries and restrict blood flow to the heart. This is called coronary artery disease, atherosclerosis or hardening of the arteries. The fatty buildup or plaque can break open and lead to the formation of a blood clot that seals the break. The clot reduces blood flow. The cycle of fatty buildup, plaque rupture, and blood clot formation causes the coronary arteries to narrow, reducing blood flow. The term "arteriosclerosis" means thickening and hardening of artery walls [20]. Arteriosclerosis involve the buildup of deposits on the insides of the artery walls, which causes thickening and hardening of the arteries. In arteriosclerosis, the deposits are composed largely of calcium. In atherosclerosis, the deposits consist of fatty substances, and artery walls lose elasticity and harden. Both arteriosclerosis and atherosclerosis affect circulation. If not taken care of they can ultimately lead to high blood pressure and to angina (chest pain), heart attack, stroke, and/or sudden cardiac death.

**Treatment**

Arteriosclerosis is a condition of clogging of the arteries. From Ayurvedic perspective, all tridoshas can manifest in this case. Kapha and Pitta types are due to fat accumulations. Vata type is from the hardening of the arteries [21-22]. Ayurvedic treatment for arteriosclerosis is similar to the treatment of heart diseases and for hypertension. Hypertension usually follows arteriosclerosis.

**Herbs**

i. Guggul lowers high cholesterol in all mind-body constitutional types. It is especially useful for Kapha. It improves circulation, reduces pain, removes accumulations and promotes healing. 1 gm. is taken in the morning and evening for 3 months.

ii. Garlic is taken along with honey.

iii. Other useful herbs are: calamus, turmeric, and elecampane, aloe vera gel with turmeric or safflower, katuka, myrrh, saffron, motherwort, and hawthorn berries. The main Chinese herbs are he shou wu (fo ti) and salvia.

**Cardiomyopathies**

These disorders fall in a single category i.e. the Vatika Hrudoga of Ayurveda. Vatika Hrudyoga comprises of an umbrella of disorders. The main features include excruciating pain in the heart, pricing, squeezing and crushing. Other features include breathlessness, feeling of emptiness in chest, palpitation, sudden lethargy, and loss of consciousness. The symptomatology explained and described in different texts conforms to the description [23].The Ayurvedic treatment comprises of Panchkarmas which mainly includes Virechna (Purgation) and Basti (medicated
enemas). Internal medicines include drugs like Ajmoda, Vishatinduka and Bold. Externally a local treatment is carried out which is a type of oleation (Snehana). This is known as Hrid-Basti. It incorporates application of oils, decoctions, juices of herbs locally on mid sternal zone, forming a wall of wet gram paste.

**Congenital Heart Disease, Cardiovascular Diseases**

Congenital means inborn or existing at birth. Most heart defects either 1) obstruct blood flow in the heart or vessels near it or 2) cause blood to flow through the heart in an abnormal pattern. Rarely defects occur in which only one ventricle (single ventricle) is present, or both the pulmonary artery and aorta arise from the same ventricle (double outlet ventricle). A third rare defect occurs when the right or left side of the heart is incompletely formed hypoplastic heart. In order to rectify the defects cardiac surgery is needed [24].

According to Caraka Samhit of Agnivesa following plants have been termed as cardiac tonic. They are as follows:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Botanical Name</th>
<th>Family</th>
<th>Synonym and useful part</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>Magnifera indica</em></td>
<td>Auacardiaceae</td>
<td>Aam, Amba, Fruit</td>
</tr>
<tr>
<td>2.</td>
<td><em>Gmelina asiatica linn, Gmelina parviflora</em></td>
<td>Verbenaceae</td>
<td>Badhar, Fruit</td>
</tr>
<tr>
<td>3.</td>
<td><em>Capparis corundas, Carissa carandas, linn</em></td>
<td>Apocynaceae</td>
<td>Karanda, Fruit, bark &amp; Leaves</td>
</tr>
<tr>
<td>4.</td>
<td><em>Garcina indica</em></td>
<td>Guttifereae</td>
<td>Amsul, Fruit</td>
</tr>
<tr>
<td>5.</td>
<td><em>Garcinia pedunculata</em></td>
<td>Guttifereae</td>
<td>Amlavettas, Fruit</td>
</tr>
<tr>
<td>6.</td>
<td><em>Ziziphus sativus, Ziziphus jujube, Ziziphus numularis</em></td>
<td>Rhamnaceae</td>
<td>Kuval, bor, Fruit &amp; Leaves</td>
</tr>
<tr>
<td>7.</td>
<td><em>Punica granatum linn</em></td>
<td>Lythraceae</td>
<td>Anardana, Flowers, Fruits</td>
</tr>
<tr>
<td>8.</td>
<td><em>Citrus medica</em></td>
<td>Rutaceae</td>
<td>Mahalung, Fruit</td>
</tr>
</tbody>
</table>

Cardiac Activity and Formulation Evaluation of Isolated Constituents of *Piper longum linn*
Some of the examples which have shown the safety and efficacy of the medicines derived from plants are:

- Artemisin (*Artemisia annua* Linn) for treatment of malaria [25]
- Isolation of camptothecin from the bark of *Camptotheca acuminata*, a proven potential antitumour and antileukemic agent developed by Indian Institute of Chemical technology [26].
- Azadirachtin an active principle of Neem (*Azadirachta indica*) isolated by National Chemical Laboratory (NCL)
- Use of digitoxin and digoxin as cardiac glycosides derived from plant digitalis.
- Vincristine and Vinblastine from *Catharanthus roseus* (Linn) for the treatment of cancer.
- Taxol from European yew (*Taxus brevifolia* Nutt) for ovarian and lung cancer.
- Etoposide – a semisynthetic anti-neoplastic agent derived from Mayapple (*Podophyllum peltatum*) useful in treatment of refractory testicular carcinoma, small cell lung carcinoma.
- ‘Gulip’ a standardized extract of *Commiphora mukul* is a hypolipidaemic agent.

These examples have proved that more focus on the research of medicinal plants will lead to the development of more potential drugs for the treatment of various serious diseases like cancer, malaria, and heart diseases.

Any deviation from the normal functioning of the heart will lead to heart disease [27] Since heart is one of the major and important organ of the body any small variation in the heart function has to be treated urgently [28-29].

### 1.5 EXISTING TREATMENT OF CARDIAC DISEASES

As per modern terminology heart diseases can be classified or divide as follows:

**Myocardial ischemia**

In this disease condition there is a deficiency of oxygen supply [30]. It is characterized by adhesion of platelets to the inner vascular wall resulting into the interference in the functioning of extrinsic or intrinsic blood clotting system. The platelets adhere to the collagen exposed due to an injury to the vascular endothelium. The release of thromboxane $A_2$ as results into vasoconstriction and enhances platelet aggregation. The permanent platelet fibrin clot initiates a series of events which leads to myocardial ischemia.
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**Congestive heart failure**

The degree of force of heart muscle contraction is governed by the external of ventricular muscle stretching [31]. The contractile power decline if the muscle fiber is stretched beyond a critical length. In certain condition; the activation of neurohumoral system (eg. Increased release of catacholamines, elevation of plasma renin activity or plasma antidiuretic hormone level) may result into increased blood volume, venous return and diastolic volume.

The heart workload increases resulting into stretching of muscle fibers beyond that critical length. If such situation remains for considerable period of time, thus leads to a progressive decline in the force of heart contraction. Blood accumulates in the heart due to its inability to eject all the blood: So the heart workload progressively increases resulting into progressive increase in the stretching of muscle fibers and failure of the heart becomes gradually pronounced. The blood starts accumulating into large veins and in the tissues, highly perfused with blood. Thus congestion of both, pulmonary and systemic circulation results into peripheral edema and diminished exercise tolerance. This situation is called as congestive heart failure. It is characterized by left ventricular dysfunction, reduced exercise tolerance and frequent ventricular arrhythmias. Generally advanced age, hypertension, diabetes mellitus and ischemic heart diseases contribute to the development of congestive heart failure [32].

**Angina pectoris**

The primary cause of angina is supposed to be arteriosclerosis of large coronary arteries. This may lead to reflex vasospasm of coronary arteries those results into sudden, severe substernal pain which often radiates to the left shoulder and along the flexor surface of the left arm. The duration of angina episode may very from 30 seconds to 30 minutes. Hypertension and cigarette smoking are amongst the principle etiologies of angina pectoris [33].

**Arrhythmias**

The rhythmic contraction of the heart is possible due to the presence of intrinsic pace makes and conduction tissues in the heart sinusatrial node (SA node) is normal pace maker because it is capable of initiating impulses which stimulate the myocardium to contract without any outside influence from the nervous system. Any deviation from the normal rhythmic motion will lead to the arrhythmia. An arrhythmia may arrest due to abnormality in a) rate, regularity or site of origin of cardiac impulse or b) conduction that causes an alteration in the normal sequence of the atria and ventricles.
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1.6 DRUGS USED IN HEART DISEASES [34]

Cardiac glycosides

a) Digitalis (b) β-Adrenoreceptor agonists (c) Bipyridine derivatives

Mode of action (MOA): -

They act by increasing the amount of intracellular calcium ions resulting into more forceful contraction of cardiac muscle [35].

Vasoconstriction – digitalis

Vasodilatation- bipyridine derivatives.

All these drugs act as inotropic agents that are they increase the force of myocardial contraction.

Antiarrhythmic agents

Based on the electrophysiological action drugs can be categorized into 4 classes [36].

Local anaesthetic drugs

The major physiological effect of this class of drugs is a reduction in the maximum rate of myocardial cell depolarization during phase “0” of the action potential without any effect on the resting membrane potential.

Accordingly the various drugs are classified as:

i. Membrane depressant drugs: Depressant of electrophysiological properties of myocardial cells e.g.: - Quinidine, Procainamide, and di isopyramide.

ii. Drugs which facilitate impulse conduction and short refractory period while depressing automaticity e.g.: - Lidocaine, Phenytoin, Tocainide, Aprindine.

iii. β-adrenergic blockers e.g. Alprenolol, Atenolol, Metoprolol, Practolol, Propanolol

iv. Amiodarone e.g. Bretylium, D-Sotalol.

v. Selective Calcium antagonists e.g. Nifedipine, Verapamil, Diltiazam

vi. Miscellaneous agents e.g. Atropine, Neostigmine.

β- Adrenergic blocking agents

Local increase in catecholamine activity that accompany centrally mediated sympathetic nervous system. Discharge or myocardial ischemia can be associated with sufficient local enhancement in automaticity so that competing rhythms and
ectopy emerge, β -blockers can supress this type of automaticity. They also can be produce direct depressant effect on myocardial cell membrane.

**Agents that prolong the action potential duration**
These agents are having ability to prolong action potential duration and hence refractory period of cardiac tissue. Bretylium and amiodarone suppress cardiac catecholamine effects that result from sympathetic nerve stimulation. This agents supress ventricular tachycardia and ventricular fibrillation.

**Sodium channel blocking agents**
Sodium entry into the myocardial cell during phase “0” of the action potential can be suppressed by administration of Tetrodotoxin or by depolarizing the cell membrane to potential less than –60 mv. These results in decrease in the slope for phase 0 of the action potential.

**Anti - anginal drugs**
These agents [37] causes redistribution of coronary blood flow to the ischemic regions of heart and also reduce myocardial oxygen demand. This later effect is produced by a reduction in venous tone due to vasodilation effect and a pulling of blood in the peripheral veins that result in a reduction in ventricular volume, stroke volume and cardiac output. It also causes a decrease in peripheral resistance during myocardial contractions. The combined vasodilatory effects cause a decrease in the cardiac workload and reduced in oxygen consumption or demand.

Classification of Anti-anginal drugs:
I) Nitrates and nitrites.
II) Xanthines (aminophyllines)
III) Nicotinic acid and its derivatives
IV) Papavarine
V) α -Adrenergic blocker
VI) MAO inhibitors

**Anti-hypertensive drugs [38-39]**
These agents lowers blood pressure to a normal level and saves patients from severe heart attacks.
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Drugs affecting Sympathetic tone :-
Drugs that alter sympathetic activity e.g. Methyldopa, Clonidine.
   i) Drugs that act as adrenergic neuron blockers. e.g. Guanethidine, Reserpine.
   ii) Ganglionic blocking drugs e.g. Trimethaphan.
   iii) α-adrenoreceptor blocking agents e.g. Prazosin, Phentolamine.
   iv) β-adrenoreceptor blocking agents e.g. Propanolol, Atenolol.

Vasodilators [40]: Direct vasodilators
   i) Arterial dilator e.g. Hydralazine.
   ii) Balanced vasodilators e.g. Minoxidil.
   iii) Calcium channel blocking agents e.g. Nifedipine.

Agents acting on renin-angiotensin system [41]
These agents act at enzymatic level and helps in maintaining normal rhythm of heart.
   i) Angiotensin antagonists e.g. Saralasin.
   ii) Angiotensin converting enzyme inhibitors. e.g. Captopril, Enalapril.

Diuretics
These agents helps in maintaining the normal blood pressure.
   i) Thiazides e.g. Hydrochlorothiazide.
   ii) Loop diuretics e.g. Furosemide.
   iii) Potassium sparing diuretics e.g. Triamterene.

Cardiac Activity and Formulation Evaluation of Isolated Constituents of Piper longum linn
CARDIOVASCULAR DRUGS

I) CARDIAC GLYCOSIDES

![Chemical structures of Digoxin and Digitoxin]

II) ANTIHYPERTENSIVE AND HYPOTENSIVE DRUGS

![Chemical structures of Clonidine and Hydralazine]

![Chemical structures of Methyldopa, Diazoxide, and Sodium nitroprusside]

Cardiac Activity and Formulation Evaluation of Isolated Constituents of Piper longum linn
III) ANTI-ARRHYMIC AGENTS

a) Membrane Stabilizing agent

Quinidine  Lorcanide

b) Antisympathetic Drugs

Propranolol

c) Prolong Cardiac Action

Amiodarone  Bretylium
d) Interference with Calcium Conductance

IV) VASOPRESSOR DRUGS

As mentioned earlier Ayurveda is playing a vital role in the treatment of heart diseases [42]. The plants which are having therapeutic activity against heart disease’s are mentioned in Ayurveda. Ayurveda has given the systematic description of the heart diseases. Different types and symptoms of the heart diseases have been documented in the Ayurvedic literature. The plants and its various combinations, formulations have been described in detail [43-47]. Many cardio- tonic plants have been given importance due to its good therapeutic action. The first few plants which are considered to be the primary basis for treatment in the heart diseases are mentioned in Caraka Samhit.

Cardiac Activity and Formulation Evaluation of Isolated Constituents of Piper longum linn
1.7 CATEGORIES OF AYURVEDIC PLANTS

Cardiotonic
These plants act as a tonic to the weak heart and they give strength [47] to the heart. This plant serves as a first line of treatment in heart diseases.

Cardiac Stimulant.
These are the plants which help in regularizing the rhythm of the heart in low and irregular heart beats of the heart in disease condition [48]. Plants and their extract in specific doses help to normalize the regular rhythm.

Cardiac depressant
They help in maintaining the normal rhythmic movement [49] of heart in excited state or in disease condition. The dose of the drug is very important.

Vasoconstrictors
Vasodilators

Table 1.2 Categories of Ayurvedic Plants

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<th>Category</th>
<th>Common Name</th>
<th>Botanical Name</th>
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<td>Terminalia arjuna</td>
<td>Combrataceae</td>
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<td></td>
<td>Vanapalandu</td>
<td>Urginea indica</td>
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<td>Karvirmul</td>
<td>Nerium indicum</td>
<td>Apocynaceae</td>
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<tr>
<td>Cardiac Stimulant</td>
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<td>Ephedra girardiana</td>
<td>Ephedraceae</td>
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<td></td>
<td>Hatpatri</td>
<td>Digitalis purpurea</td>
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<td></td>
<td>Suchi</td>
<td>Atropa belladonna</td>
<td>Solanaceae</td>
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<td>Cardiac Depressant</td>
<td>Ahifen</td>
<td>Papaver somniferum</td>
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<td></td>
<td>Vatsnabh</td>
<td>Aconitum ferox</td>
<td>Renunculaceae</td>
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<tr>
<td></td>
<td>Kupilu</td>
<td>Strychnous nuxvomica</td>
<td>Loganiaceae</td>
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<tr>
<td>Vasoconstrictors</td>
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<td>Som</td>
<td>Ephedra girardiana</td>
<td>Ephedraceae</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Sarpagandha</td>
<td>Raulfia serpentina</td>
<td>Apocynaceae</td>
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</tbody>
</table>
According to Ayurveda, heart diseases can manifest in any of three doshas (vata, pitta and kapha). Vata types manifest more in old age where there is drying out of the tissue and hardening the arteries. Pitta types manifest with anger, irritability, excess ambition. Kapha types manifest with accumulation of mucus, fat and cholesterol which obstructs heart function. Besides above mentioned plants, many plants are mentioned in Ayurveda which exert good pharmacological activity in heart diseases. Ancient literature gives information regarding symptoms of heart diseases, various plants used alone or in combination which exerts beneficial activity.

1.8 PLANTS PRESCRIBED IN AYURVEDA FOR CARDIAC DISEASES

**Aconitum ferox**

Family: Renunculaceae; Synonym: Bachnag, Vastanabh

Used part: Root

They occur in the region of Gadhwal to Sikkim till the five thousand meter heights. In the pure form it is cardiac stimulant. When taken along with milk it provides strength to the heart. It also increases the blood pressure and regularizes the breathing. It lowers the swelling in heart diseases.

**Allium sativum**

Synonym: Lahsun (Garlic); Used part - Stem and oil.

Garlic is combating fungal infections, lowers blood pressure, boost the immune system, fights infections, and helps in the prevention of some forms of cancer [50]. It is also believed that garlic may interfere with the metabolism of cholesterol and aid with lowering the over all cholesterol count. Garlic comes in many different forms including fresh herb or clove, liquid, oil, powder and capsules. When taking garlic one should look be sure that it supplies at least 4000 milligrams of allicin per pill, which is the amount of allicin provided by one fresh garlic clove. In a supplement, between 400 to 600 milligrams of garlic per day will help combat colds and the flu [51].

Louis Pasteur proved that garlic had antibiotic properties by putting a small piece in a petri dish of bacteria, which it quickly killed. That was the first of thousands of modern scientific experiments using garlic. It also is helpful against parasites, bacterial infection, cancer, ulcers and even slows the growth of existing tumors. Garlic [52-53] can be used to lower cholesterol. It is useful in alleviating vata doshas controlling blood pressure. A paste made of about 1 gm of garlic should be mixed with a glass of buttermilk and can be taken twice a day. It is helpful in lowering blood pressure [54-55] and lowers triglycerides that have impact on heart diseases.
Atropa belladonna [56]
Family: Solanaceae; Synonym: Suchi
Useful part: Root and Leaves
It is found in South America, some parts of Kashmir. It is a cardiac stimulant in powder form it can be given in 30 to 60 mg dosage. It is also used as antidiuretic.

Azadirachta indica or Neem:
May benefit coronary artery disease and heart arrhythmias [57], in addition to protecting against ulcers and strep infections [58].

Carum roxburghianum
Family: Umbellifereae; Synonym: Ova
Useful part: Fruit.
It occurs widely throughout India. Due to its properties it is used in Vataj type of heart diseases to strengthen the heart. It acts as a cardiotonic. It is generally given in 1 to 2 gm. quantity.

Cassia fistula [59]
Family: Leguminaceae; Synonym: Bahava
Useful part: Fruit, leaves.
It is found throughout India. It is used in pitaj type and it reduces pain in heart diseases. It can be given along with honey. The fruit powder can be given in 5-10 gm.

Centella asiatica or Mandukaparni
The plant has shown promise in cognitive, circulatory and even digestive health. C. asiatica has been shown to help patients with venous hypertensive microangiopathy [60]. Doses as high as 120 mg/d may be used safely, researchers noted. In another study of patients with venous hypertension, treatment with the triterpenic fraction for four weeks improved symptoms [61]. Significant changes occurred in terms of swelling sensation, restless lower extremity, pain and cramps, and tiredness after doses of either 60 mg or 30 mg three times daily. In microangiopathy in diabetics, the triterpenic fraction (60 mg twice daily for 12 months) decreased capillary filtration and edema, which in turn improved the condition [62].
Cinnamon
Botanical Name: *Cinnamomum Zeylanicum*; Synonym: Dalchini
Useful part: Fruit.
Two tablespoons of honey and three teaspoons of Cinnamon Powder mixed in 16 ounces of tea water, if given to a cholesterol patient, it reduces the level of cholesterol in the blood by 10% within 2 hrs. A paste of honey and cinnamon powder, apply on bread or chapatti instead of jelly and jam and if eat regularly for breakfast. It reduces the cholesterol in the arteries and saves the patient from heart attack [63] relieves loss of breath and strengthens the heartbeat.

*Citrus medica*
Family: Rutaceae; Synonym: Mahalung
Useful part: Fruit
It is found in Sikkim, Assam, Madhya Pradesh and Sahydri region. It is a cardiotonic. The fruit of the plant is beneficial in strengthening the heart.

*Convolvulus pluricaulis Choisy* or Shankhpushpi
Latin name: *Convolvulus pluricaulis Choisy* (Syn. C. microphyllus Sieb, ex Spreng)
Family: Convolvulaceae , English name: Aloe weed
Improves Kapha-vata-pitta doshas and the herb is astringent and bitter. Chemical studies of whole plant have shown the presence of glycosides, coumarins, flavonoids and alkaloids. Shankha pushpine, (the alkaloid) has been identified as active principle. Sitosterol glycoside, hydroxy cinnamic acid, octacosanol tetracosane along with glucose, sucrose also have been isolated from the plant drugs. There is a pertinent reference in Ayurvedic literature about the use of the drug as brain tonic in hypotensive syndromes. The pharmacological studies of the herb have shown varying degree of its hypotensive and tranquilizing effects. Clinical studies have exhibited demonstrable beneficial effects in the patients of anxiety neurosis. The herb induces a feeling of calm and peace, good sleep and a relief in anxiety, stresses, and mental fatigue, producing a significant reduction in the level of anxiety, neuroticism arising due to various levels of stresses. The herb appears to produce its action by modulation of neuro-chemistry of the brain. Further, the herb is non-toxic and its use does not produce any side effects.

*Crategus* or Hawthorn Berry
The hawthorn tree, with its bright red berries and long needlelike thorns, is a member of the rose family. Its flowers, leaves and fruit are used to make an herbal extract
valued for its heart-strengthening properties. Studies show that crataegus tincture strengthens heartbeat and improves circulation in the blood vessels of the heart. Hawthorn extract gently dilates the coronary vessels increasing the supply of arterial blood to the heart. This action enhances oxygen utilization, resulting in a stronger and more powerful heart muscle.

Regular intake of crategus regulates heart rate and reduces the feeling of anxiety and pressure around the heart so often reported by cardiac patients. Crategus differs from digitalis, which is also an effective heart stimulant, in that it does not produce side effects. The overall effect of digitalis is strengthened by crateagus [64]. Hawthorn is one of the most studied plants in phytotherapy; in many countries it is recognized as a pharmaceutical.

**Digitails purpurea [56,65]**

Family: Scrophulariaceae; Useful part: Leaves

It is found in Kashmir, Darjiling an Nilgiri mountain. In the larger dosage form it acts as a cardiac stimulant however careful monitoring is very essential. It regulates the blood pressure and helps to strengthen the heart.

**Embilica officinalis**

Family: Euphorbiaceae; Synonym: Avia, Shreefal

Useful part: Fruit.

It is found till 1500 meters height throughout India. It is mostly used in all the types of heart diseases. It is given along with honey and sugar. The fruit powder is given in the dose of 1 to 2 gm. It is used to rebuild and maintain new tissues and increases red blood cell count. It is the highest natural source of vitamin C. It reduces pitta without aggravating vata or kapha.[66]. In Ayurveda, Amla fruits are reputed Rasayanas and rejuvenators. They are extensively used in Ayurvedic preparations for the treatment of a number of diseases and debility states and are one of the three constituents of Triphala, which is a remedy for constipation, indigestion [67] and hyperacidity. Fruits of the herb pacify and normalise imbalance and vitiation in Vata-pitta-khapha doshas. They are astringent, refrigerant, digestive and tonic.

Chemical studies [68] have isolated gallic and ellagic acids, hydrolysable tannins, ascorbic acid (Vitamin C), phyllembic acid embicol, alkaloids. The fruits (pulp), on analysis, have been found to contain mineral matter (0.7%), protein (0.5%), carbohydrates (14%), calcium (0.05%), phosphorous (0.02%), iron (1.2 mg/100g), nicotinic acid (0.2 mg/ 100g), and vitamin C (600-900 mg/100g) and are extensively used as nutritious, restorative food supplements, supplying dietary substances in alleviating toxicides in body functions.
This plant has shown its mettle in the areas of digestive and heart health [69], in addition to benefiting cancer patients and diabetics. It reduces solid tumors when given alongside chyavanaprash [70-71]. Plant even help to reduce the toxic side effects of chemotherapy. An aqueous extract of *E. officinalis* was seen to offset the adverse effects associated with cyclophosphamide, a popular anticancer drug, which has side effects that include hematoxicity. The extract, given at a dose of 100 mg/kg for 10 days, restored antioxidant status to the kidneys [72]. In diabetics, the methanolic extract of *E. officinalis* was seen to reduce blood sugar levels in diabetic rats when given in doses of 100 mg/kg [73]. They have potent immunomodulatory and immunostimulant activities, antipyretic, spasmyloytic, antifungal, antibacterial and antiviral activities.

**Ephedra girardiana**

Family: Ephedraceae; Useful part: Stem.

It is found in the Himalaya till 2000 meter height. It is useful in regularizing the breathing in heart diseases. It is given in the powder form in the quantity 0.5 gm. to 1 gm.[74]

**Garcinia pedunculata**

Family: Guttifereae; Useful part: Fruit

Synonym: Amlavelatts

It is found in the forest region of Asam and Manipur till two thousand meter height. In the fruit the acidic components is found in large quantity and it is more acidic in nature. It acts as a cardiac stimulant and use in heart diseases to strengthen the heart [75].

**Gymnema sylvestre**, Meshasringa

Shows hypoglycemic and anti-hyperglycemic activity, which may be useful for diabetics [76].The botanical may also aid with cholesterol levels and even weight loss. Researchers from Shinshu University in Japan reported an extract of *G. sylvestre* leaves given to rats for three weeks influenced lipid metabolism, improving serum cholesterol and triglyceride levels [77].

**Pokharmul**

Botanical Name: *Inula racemosa*; Family: Compositeae

Useful part: Root
Occurs in the North and Western parts of Himalaya. Due to the beneficial pharmacological properties of this plant it is used as cardio stimulant and cardiotonic to strengthen the heart. It helps in lowering the cholesterol levels and regularize the breathing. It is given along with honey in the quantity of 1-3 gms [78].

*Mucuna pruriens* known as Kapikachchha

The plant exhibits potential benefits in the realms of heart disease and diabetes. Alcohol extract of *M. pruriens* inhibited lipid peroxidation, a factor in free radical damage and heart disease [79]. The extract had an anti-lipid peroxidation property, due to its effect in removing hydroxyl radicals and superoxides. In other Indian research, two studies showed alcohol extracts of *M. pruriens* benefited diabetes. In a rat model, 200 mg/kg lowered serum glucose levels while helping to prevent diabetes-related cataract development. Research also indicated that 200 mg/kg/d may exert its maximum anti-hyperglycemic effects after six weeks [80].

*Nerium indicum*

Family: Apocynaceae; Synonym: Karvir.

Useful part: Root

Plant is found from Nepal to Kashmir till 2100 meter height, and also found in Mahya Pradesh. Its actions on the heart are same as that of the digitalis. It improves the digestion process of heart and gives strength to the heart. However when taken in larger quantity (more than 30-125 mg) it causes toxic effects on heart, it weakness the heart muscle which leads to decrease in the normal functioning of heart and ultimately the death.

*Ocimum sanctum linn*

Family: Lamiaceae (Labiatae); Synonym: Holy basil

Useful part: Leaves

This medicinal herb is used against a wide variety of diseases [81]. Indian Materia Medica describes the use of the herb in the treatment of ailments like bronchitis, rheumatism, pyrexia (fever) and coryza. Tulsi leaves are household remedy for common cold and cough. Ayurvedic text describes the herb to be aromatic and a pacifier/ normaliser of vitiated and deranged Kapha-vata doshas and is useful in blood disorders (Raktavikar). Phytochemical investigations of leaves have shown the presence of flavones, glycosides, gallic acid and its ester, caffeic acid and volatile oil having eugenol (70.5%) as the main component. Studies with seeds have afforded triglycerides and fixed oils having linoleic acid (52.23%) and linolenic acid (16.63%) as major unsaturated fatty acids. These fatty acids are essential for human nutrition, and the mixtures are used as dietary supplements.

*Cardiac Activity and Formulation Evaluation of Isolated Constituents of Piper longum linn* 24
Pharmacological studies and biological evaluations of Tulsi leaves extracts (aqueous and ethanol) have shown adaptogenic properties, which improve endurance and resistances when tested against a battery of stress-induced conditions indicating non-specific mode of actions. Leaves and seeds of the herb (extracts and volatile and fixed oils) possess antiinflammatory and antiasthmatic activities. Anti-inflammatory activities antagonise initiated inflammatory chemical mediators. Plant lowers stress-induced cholesterol level, analgesic, antipyretic, antibacterial, antifungal, antiviral, antiarthritic, immunostimulant activities without any noticeable toxicity.

**Papaver Somniferum**

Family : Papaveraceae; Synonym : Afu

Useful part : Fruit and Seed.

It occurs in Europe, North Africa. In India it is found in Uttar Pradesh, Bengal, Bihar and Madhya Pradesh. It act as cardiac depressant.

**Picrorhiza kurroa Royal ex. Benth** or Kutaki

Latin name : *Picrorhiza kurroa* Royal ex. Benth.; Family : Scrophulariaceae,

English name : Indian gentian , Useful part : Root.

Root (rhizome part) of the herb comprises the drug, and used for the treatment of fever, jaundice, liver afflictions, bile disorders and against infections, inflammatory and drainage morbid conditions[82]. The herb pacifies the vitiated Kapha-vata doshas and corrects imbalance in them. It is astringent, bitter and a valuable tonic, extensively employed for rejuvenation therapy.

Phytochemical studies of the herb (Kutaki) have shown the presence of phenolic glycosides (androsin-aglycone, apocymine), iridoid glycosides (kutkoside, picrosides I, II, III), cucurbitaceous glycosides, vinallic acid, cinnamic acid. Various pharmacological studies carried out in different set of parameters have confirmed the medicinal utility of the herb. Active constituents of the herb have been found to be responsible for the inhibition of free oxygen radicals (Reactive oxygen species - ROS) from activated polymor-phonuclear (PMN) leucocytes, which affect inflammatory conditions, validating therapeutic potentiality of the herb in immune disorders.

Picroliv - a standardised fraction from root shows hepato-protective activity against liver cirrhosis and liver toxicity, promoting the repair of injured tissues. The standard fraction Picroliv also has exhibited hypolipidaemic action, altering lipolytic activities in plasma, liver, heart and adipose stimulating catabolism of riskly low-density lipoprotein (LDL) while increasing the beneficial high-density lipoprotein (HDL) fraction. Roots also shows antiasthmatic activity. Toxicity study has shown that the herb is non-toxic in nature. LD₅₀ (Median lethal dose in 50% experimental animals)
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of the herb (root) in albino mice (wt. 20-25g) has been calculated to be more than 1000mg/kg administered intraperitoneally. While LD50 of picroliv has been found to be 2500mg/kg P.O. (administered orally). These toxicity measures are much higher than silymarin, suggesting a better therapeutic index of picroliv and kutaki.

**Phoenix sylvestris**

Family : Palmeae; Synonym : Khajur

Useful part : Fruit

It is found throughout India, North Africa, Egypt, Syria. It is used in Pitaj type of heart diseases. It is used to strengthen the heart and regulate the blood pressure. The extract of fruit is given in the 50-100 ml. dose.

**Piper longum linn / Pippali Mul**

Family : Piperaceae

Piper longum root powder along with honey is useful in Vata type of heart isease. It helps in lowering cholesterol levels [83-84].

**Rauwolfia serpentina**

Family : Apocynaceae; Synonym : Sarpagandha, Adkae

Useful part : Root

It is found throughout India, Bihar, Bengal, Uttar Pradehs, Brahmadesh, Srilanka and Java. It is useful in the regulation of blood pressure. It decreases blood pressure in the dosage of 0.5 to 1 gm [85]

**Santalum album**

Family : Santalaceae ; Synonym - Chandan

Useful part : Stem & Oil.

It is found in Karnatakka, Keral Tamilnadu. Oil of this plant is very useful. It is giving strength to the heart muscles increases force and stabilizes heart. It is given along with sugar in the powder form it is given in the quantity 1 to 3 gram [86].

**Sida cordiofolia**

Family : Malvaceae; Synonym : Chikana

Useful part : Root and leaves.

Cardiac Activity and Formulation Evaluation of Isolated Constituents of *Piper longum linn* 26
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It occurs throughout India till 1200 meters. It increases the heart force and acts as cardiotonic. Useful in pitaj type of heart disease. It regulates the blood pressure. The root and leaf powder is given in the dosage form of 3 to 6 gm in divided dosage.

*Strychnous nyxvomica*

Family : Loganiaceae; Synonym : Kuchala

Useful part : Seed.

It is found in tropical forest of India specially in Bihar, Kerala, Konkan, Orisa. Shrilanka. It is a Vasocostrictor regulates the blood pressure and can be used as cardiac stimulant. In powder form it is given in 60 to 250 mg in divided doses.

*Arjuna (Terminalia Arjuna)*

Botanical Name - Terminalia Arjuna ; Family : Combrataceae

Synonym : (Marathi) Arjuna, Sardhol, Saldhaval.

Source : Himalaya, Bengal, Bihar and Mountain region in Madhya Pradesh.

*Arjuna* is a big tree and its bark is used as medicine [87]. Arjuna is a cardiac stimulant and useful for hemorrhages, diarrhea, and poison antidote (scorpion-sting). It is most popularly used for heart diseases complicated with endocarditis, mitral regurgitation, pericarditis, angina an hemoptysis. Arjuna herb on a regular bases strengthen the heart and has been used for thousands of years for heart diseases with no side effects. The powder or decoction of its bark is given to the patient during and even after the attack.

The powder is given to the patient in a dose of 1 gm., four times a day. If the heart disease is of *vatika* type, it is mixed with ghee. If it is of *paittika* type, then milk is used. In *kaphaja* type of heart disease it is mixed with honey or *pippali* powder. For decoction usually 30 gm. of the raw powder of the bark of the drug is boiled with approximately 500 ml. of water and reduced to one-fourth. This is then filtered, honey or ghee is added to it, and given to the patient. With honey, the decoction should become cold before mixing. Ghee is mixed, when the decoction is warm, and is given to the patient as such. There are many preparations of this drug.

*Arjunarishta* is commonly used by physicians [88]. Six teaspoonfuls of this liquid drug are given to the patient twice daily after food with an equal quantity of water. *Arjuna* is boiled in cow’s ghee, and this medicated ghee is given to the patients in a dose of 1 teaspoonful twice daily on empty stomach, mixed with a cup of warm milk. This preparation is known as *Arjuna ghrita*. This medicine should not be given to a person having a fat body. This is likely to add to his fat and may create more problems. Arjuna is a famous cardiac tonic [89] used in Ayurveda for a variety of heart conditions, used to lower blood pressure and heart rate. Traditionally given to
support circulation and oxygenation of all tissues. Often combined with ashwagandha, brahmi and guggul in heart formulas.

Arjuna Rasayana is especially good for the aged and can be used for all heart conditions. This herb contains unusually large quantities of calcium. Arjuna has been described as a cardiac tonic named 'Nadisarjja' in ancient Indian scriptures. A great restorative, Arjuna soothes both physical and emotional hearts. It calms an aggravated sadhaka pitta, slowing down the release of toxic hormones. Arjuna has the unique ability to balance all three doshas: vata, pitta and kapha. Recent research has revalidated Arjuna's role in promoting cardiovascular health. Arjuna is a coronary vasodilator. It protects the heart, strengthens circulation, and helps to maintain the tone and health of the heart muscle. It is also useful in stopping bleeding and to promote healing after a heart attack.

Dose: 1/2 teaspoon (500 milligrams to one gram) 3 times a day with honey and warm water.

It is found that the plant, with its arjunic and terminic acids, glycosides and antioxidants, decreased the frequency of angina when given in doses of 500 mg every eight hours for one week. The dose also decreased the need for isosorbide dinitrate, an anti-anginal prescription medication. Arjunolic acid, an Arjuna triterpene and a potent part of the Arjuna bark, may also offer cardiac protection. Administered at a dose of 15 mg/kg, arjunolic acid [90] could protect against damage wreaked by myocardial necrosis, which translates into irreparable damage to heart cells. Dried pulverized T. Arjuna L. bark may prevent oxidative stress. Given in two doses (500 mg/kg or 750 mg/kg) six days per week for 12 weeks to laboratory rats, the compound protected against ischemic-reperfusion injury, which is characterized by damage usually caused by heart surgery.

**Giloe/Guduchi**

Latin name: *Tinospora cordifolia* (Willd) Miers; Family: Menispermaceae

English name: Heart-leaved moonseed

The drug, consisting of stems of the herb, restores a balance among the vitiated and deranged Kapha, Vata and Pitta doshas and is alterative and bitter. Categorised in Ayurveda as Rasayana, the herb is used in inflammation, rheumatism, diabetes, jaundice and allied liver problem and malarial fever [91]. Chemical investigations of the stems have isolated compounds, broadly classified as alkaloids (berberine), glycosides (furanoid diterpene glycoside), lactones (Tinosporon, tinosporide), stearols and fatty acids. They are found to be rich in calcium (1.06%). Trace elements—manganese, zinc, copper and cobalt are also reported. *T. cordifolia* herb possesses potent immunono-dulatory and immuno stimulant activities. It produces significant leucocytosis (increased number of leucocytes in blood) in response to infection and predominant neutrophilia affording an increased protection against susceptibility to pathogenic infections.
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The herb is an adaptogen, with potent adaptogenic activities. It induces a marked protection against restraint stress-induced ulceration and other stress-mediated effects. Utility and therapeutic value of the herb has been demonstrated in various liver disorders including jaundice. Improper sugar (glucose) metabolism at times causes a diabetic condition. Use of the herb has been found to modify the metabolism, exhibiting its antihyperglycaemic activity [92]. Toxicity study has shown the herb to be non-toxic with wide safety margin [93]. Maximum tolerate dose (MTD) of stem and whole plant in albino mice (20-30g wt) has been calculated to be 250mg/kg and 500mg/kg respectively administered intraperitoneally.

_Urginea indica_

Family: Liliaceae; Synonym: Vanapalandu, Rankanda

It is found in the Western part of the Himalaya till 2000 meter height, in Konkan and Chhota Nagpur region. In the large quantities it acts as a cardiotonic and cardiostimulant. It also has a diuretic property. In the powder form it is given in the quantity 0.1 gm. to 0.2 gm daily [94].

_Vitis Vinifera_

Family: Vitaceae; Synonym: Draksha

Useful part: Fruit.

It is found in North-Western parts of India, Afghanistan. It is use in pita type of heart diseases. It helps to strengthen the heart.

_Withania somnifera_

Family: Vitaceae; Synonym: Ashwagandha

Plant is a jack-of-all-trades herb. Its ability to increase nitric oxide production explain its immunostimulatory properties, and it appears to exert a positive influence on the endocrine, cardiopulmonary and central nervous systems. Ashwagandha root extract in 50 mg/kg, 100 mg/kg and 200 mg/kg doses per day over a week also found to improve memory in rats [95].
Table 1.3 Plants in Ayurvedic Pharmacopoeia [96-98]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Botanical name</th>
<th>Plant part used</th>
<th>Design and model</th>
<th>Result</th>
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<tbody>
<tr>
<td>1</td>
<td>Azadirachta indica</td>
<td>A decoction of Azadirachta indica, Boerhaavia diffusa, Cedrus deodar, Picrorhiza kurrooa, Terminalia chebula, Tinospora cordifolia, Trichosantes lobata; Inula racemosa</td>
<td>14 cases of congestive heart failure</td>
<td>All patients were given the decoction and Urgenic indica. Patients with ischemic heart disease, cardiomyopathy and cor pulmonale were given powder of Inula racemosa, while patients with rheumatic heart disease were given Commiphora mukul. After 2 weeks of treatment all 10 patients were cured completely 2 had bradycardia and 2 were refractory.</td>
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<tr>
<td>2</td>
<td>Cassia fistula</td>
<td>Legume Cassia fistula</td>
<td>Albino rats</td>
<td>Administration of Cassia fistula produced a significant decrease in blood and liver total lipids. Brain, spleen, kidneys and heart followed a similar trend but with moderate effect. Blood, liver kidneys, spleen and heart total cholesterol significantly decreased. The level of triglycerides was markedly improved.</td>
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<tr>
<td>Sr. No.</td>
<td>Botanical name</td>
<td>Plant part used</td>
<td>Design and model</td>
<td>Result</td>
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<td>3</td>
<td><em>Foeniculum vulgare</em></td>
<td>Aqueous extracts of <em>Foeniculum vulgare</em> leaves were lyophilized and boiled</td>
<td>Pentobar-bital Anaesthetized rats</td>
<td>Intravenous administration of extract produced a significant dose-related reduction in arterial blood pressure, without affecting the heart rate or respiratory rate. The non-boiled aqueous extract showed very little hypotensive activity.</td>
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<td>4</td>
<td><em>Cocos nucifera</em></td>
<td>Coconut and coconut oil</td>
<td>Clinical Trial: 32 coronary heart disease matched healthy controls.</td>
<td>Consumption of coconut oil was found to be similar in both groups. The groups did not differ in the fat, cholesterol consumption. The result imply no specific role for coconut or coconut oil in the causation of coronary heart disease in this set of patients.</td>
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<td>5</td>
<td><em>Elephantopus scaber</em></td>
<td>Aqueous and hydroalcoholic extracts of of whole plant of <em>Elephantopus scaber</em>. Dose: 0.3–6 g/kg</td>
<td>Mice, rats</td>
<td>Both extracts induced writhing, loss of muscle tone and death. Both reduced brewer's yeast-induced hyperthemia but when given orally did not affect it. Aqueous extract reduced intestinal transit time while the hydroalcoholic extract increased it. Given IV, blood pressure and heart rate were reduced.</td>
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<td>Botanical name</td>
<td>Plant part used</td>
<td>Preparation and dosage</td>
<td>Design and model</td>
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</tr>
<tr>
<td>6</td>
<td><em>Myristica fragrans</em> Houtt</td>
<td>Ethanolic extract of <em>Myristica fragrans</em></td>
<td>500 mg/kg orally for 60 days</td>
<td>Albino rabbits and controls</td>
</tr>
<tr>
<td>7</td>
<td><em>Tribulus terrestris</em></td>
<td>Saponin of <em>Tribulus terrestris</em></td>
<td>Controlled clinical trial: 406 cases of angina pectoris, 67 treated as controls</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><em>Terminalia arjuna</em></td>
<td><em>Terminalia arjuna</em> bark</td>
<td>500 mg, 8 hourly</td>
<td>Clinical randomized controlled double-blind trial: 12 with congestive heart failure</td>
</tr>
<tr>
<td>Sr. No.</td>
<td>Botanical name</td>
<td>Plant part used Preparation and dosage</td>
<td>Design and model</td>
<td>Result</td>
</tr>
<tr>
<td>---------</td>
<td>----------------</td>
<td>----------------------------------------</td>
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<td>--------</td>
</tr>
<tr>
<td>9</td>
<td><em>Terminalia chebula</em></td>
<td>A decoction of the following herbs <em>Azadirachta indica</em>, <em>Boerhaavia diffusa</em>, <em>Picrorhiza kurrooa</em>, <em>Terminalia chebula</em>, <em>Tinospora cordifolia</em>, <em>Trichosantes lobata</em>, <em>Commiphora mukul</em>, 1/2 g 8 hourly; <em>Urgenic indica</em> 100 mg, 8 hourly</td>
<td>14 cases of congestive heart failure</td>
<td>All patients were given the decoction: and <em>Urgenic indica</em>. Patients with ischemic heart disease, cardiomyopathy and cor pulmonale, were given powder of <em>Inula racemosa</em>, while patients with, rheumatic heart disease were given <em>Commiphora mukul</em>. After two weeks of treatment all 10 patients were cured <em>Inula racemosa</em> 2 g, 8 completely, 2 had bradycardia, and; 2 were refractory.</td>
</tr>
<tr>
<td>10</td>
<td><em>Nelumbo nucifera</em></td>
<td>Nefereine, alkaloid extracted from the green seed embryo of <em>Nelumbo nucifera</em>. Dose of 1–10 mg/kg IV</td>
<td>Cats</td>
<td>The results indicate that neferine and quinidine have similar effects on heart electromechanical activity.</td>
</tr>
</tbody>
</table>
1.9 AYURVEDIC FORMULATION

The principles underlying Ayurvedic formulations can be broken into four parts: synergy, opposition, protection and enhancement. Synergistic formulas combine herbs with different attributes to attack conditions from many different angles. Opposition formulas include herbs with the opposite action as the main ingredient, to reduce any potential side effects. Protective combinations contain certain ingredients that act as a laxative or diuretic to combat the possibility of toxin build-up. Lastly, enhancing combinations have ingredients added that will increase the absorption and bioavailability of other key ingredients. The various formulations used in heart diseases are as follows [99-103].

Chandraprabha: A traditional formula used to maintain healthy cholesterol levels and blood sugar levels.

Abana contains arjuna, ashwaganda, shatavari. Promotes healthy cholesterol levels, helps regulate blood pressure and supplies needed oxygen to the heart. Abana regulates serum lipids by lowering the cholesterol, triglyceride, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) levels, and restores the cardioprotective high-density lipoprotein (HDL) level. Abana also reduces platelet aggregation. Moreover, Abana reduces the sensitivity of the heart to adrenergic stimulation. Abana improves the contractility of the heart by exerting a positive ionotropic action. Thus Abana produces cardioprotection. Abana tablet.

Digest Ease is a digestion formula for pitta. It supports proper digestion and absorption for individuals prone to hyperacidity and heartburn.

Heart Formula contains arjuna, bala and hawthorn berry to nourish and strengthen the heart muscle, stimulating circulation and oxygen flow. It promotes healthy cholesterol levels aiding in the defense of heart disease.

Arjun (Koha) Paste- 3 oz, 100 % Natural - This formulation is helpful in heart diseases, acne, diarrhea.

Cholest Control, 390 mg - 60 Caps, 100% Natural - Cholest Control, a perfectly blended ayurvedic herbal formulation, helps to naturally and safely reduce cholesterol levels in the body.
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Guggulu (Guggul), 475mg - 50 Caps, 100% Natural - Guggul is an Ayurvedic herb shown to be effective for arthritis, bronchitis, atherosclerosis, diet & weight loss, stress, and ulcers.

Avipattikar Churna: (Vindanga, Shankara, Lavanga, Pipli, Trifala, Mustaka, Ela, Tejpata, Kala Mirch). According to Ayurveda, it is effective in acidity, heartburn, gastritis, anorexia, loss of appetite, constipation, and hyperactivity.

Bala: According to Ayurveda, Bala is commonly used for heart diseases, soothing for arthritic pain, rejuvenative, nutritive, and stimulant for the heart, helps in the inflammation of nerve tissue. Bala pacifies high vata-pitta conditions.

Haritaki: Haritaki, 450 mg - 50 Caps, 100% Natural historical Ayurvedic uses suggest Haritaki to be used in cough conditions, asthma, abdominal distention, tumors, heart disease, skin disease and itching.

Tribulus Terrestris - 500 mg, 100 Capsules.

Cardoclear: It regularizes function of heart, maintains lipid and cures heart diseases. Capsule is compulsorily taken with milk only. Each capsule contains Arjun Panchang (300 mg), Hanuman Fal Bhasma (150 mg), and Lindipiper (50 mg) Doses: 1 or 2 capsule capsule three times a day.

Hriday Amrit - 100% natural remedy for coronary heart disease & other cardiac disorders. Ayurvedic rejuvenative "Rasayana" for congestive heart failure. Hriday Amrit is composed of herbal extracts of Arjuna (Terminalia arjuna), Punarnava (Boerhaavia diffusa), Chitrakmool (Plumbago zeylanica), Haritaki (Terminalia chebula), Ashwagandha (Withania somnifera), Nirgundi (Vitex negundo), Rasna (Vanda roxburghii), Makoi (Solanum nigrum), Guduchi (Tinospora cordifolia), Long pepper (Piper longum), Nagarmotha (Cyperus scariosus), and Viavidang (Embelia ribes)

Regular Dosage: 2 tablets twice a day. Maintenance Dose: 1 tablet twice a day.

Art Capsules Combination of garlic, hawthorn, passion flower extract and vitamin E.

MuktaVati can be taken along with any medicine being taken by the patient, does not cross-react & does not induce any side effects. It contains: Brahmi (Bacopa monieri), Shankhapushpi (Evolvulus alsinoides L.), PushkarMool (Incule racemosa), Jyotishmati (Celastrus paniculatus), Ashwagandha (Withania somnifera), Gazoban (Onasma bracteatum), Tinospora cordifolia (Guduchi), Red Coral Powder and Pearls (Mukta pishiti). Various herbs that make MuktaVati a powerful herbal remedy for high blood pressure: remedy for Hypertension, Anxiety and Insomnia. Dosage: 2 tablets twice a day (taken one hour before break fast and dinner).

Hinguvachaadi Gulika

Used in Hrut soola (Pain in the heart), paarswa soola (pain on the sides), prushta soola (back pain), kukshi rogas, Vaayu kshobham (vata imbalance due to shock), aama, kapha rogas (kapha predominant disorders), mootra kruchram (difficulty in passing urine), gulmam (Bloating), vata, vid, mootra bandham (blockage of flatulence, faecal materiel and urine), hrudrogam (heart diseases), paadu rogam (anaemia), arsas (Haemorrhoids), hidhuma (hiccups), vrudhi (Hernia), aaanaham (distension of stomach and abdomen), agnimaandyam (weak digestion), swaasam (Respiratory disorders), kaasam (cough).

Arjuna Nectar very useful in balancing or decreasing vata dosha, to help regulate blood pressure, heart muscle strengthener, improving poor blood circulation, increase red blood cell count, coronary heart disease, heart palpirations, irregular heartbeat, atherosclerosis, and angina pectoris.

Parthadyarishtam - Containing the famous heart tonic herb Arjuna, this is prescribed in the Bhaishajya Ratnavali for heart and lung diseases, as a cardiac stimulant and for controlling blood pressure.

Hridayarnava rasa and Prabhakara vati: These medicines are available in the form of tablets. Two tablets are given to the patient, three or four times a day, depending on the seriousness of the disease.

Mrigamadasava is the ideal drug at the time of acute attacks. It is a liquid medicine and given to the patient in a dose of ½ to 1 teaspoonful mixed with equal quantity of water. These medicines are to be used even after the attack has subsided. On exertion the patient may get the attack any time. It is, therefore, necessary for the patient to use the medicines mentioned above for about 6 months continuously.
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The Blissful Joy herbal supplement is another superb restorative. It is a careful blend of Arjuna, Ashwagandha (Winter Cherry) and other nourishing herbs, helps the heart by balancing Sadhaka Pitta in times of emotional stress.

1.10 THERAPEUTIC CATEGORY OF PLANTS ACTIVE IN HEART DISEASES

Hypertensives and Cardiotonics

1) Aegle marmelos (Root bark, Family: Rutaceae, Bael)
2) Allium cepa (Bulbs, Family: Liliaceae, Onion)
3) Allium sativum (Bulbs, Family: Liliaceae, Garlic)
4) Arachis hypogaea (Pods, Family: Leguminosae, Groundnut Pods)
5) Asclepias curassavica (Root, Family: Asclepiadaceae, Jakundi)
6) Coleus forskolii (Family: Labiatae, Foreskolin)
7) Capsaicin From Capsicum Spp. (Fruit)
8) Crataegus oxyacantha (Leaves, Flowering Tops, Berries, Family: Rosaceae)
9) Cucurbita maxima /pepo (Seeds, Family: Cucurbitaceae, Pumpkin seeds)
10) Daucus carota (Seeds, Family: Umbelliferae, Carrot seeds)
11) Hibiscus rosasinensis (Flowers, Family: Malvaceae, China rose)
12) Nerium indicum (Leaf and Root, Family: Apocynaceae, India oleander, Karavira).
13) Piper aurantiacum (Fruit, Family: Piperaceae)
14) Rauwolfia serpentina (Root, Family: Apocynaceae, Rauwolfia, Sarpgandha)
15) Sapindus trifoliatus (Fruits, Family: Sapindaceae, Ritha)
16) Emblica officinalis (Fruit, Family: Euphorbiacea, Amla, Amlaki).
17) Terminalia arjuna (Bark, Family: Combretaceae, Arjuna)
18) Terminalia chebula (Fruit, Family: Combretaceae, Myrobalan)
19) Tribulus terrestris (Fruit, Family: Zygophyllaceae, Tribulus, Gokhru)
20) Urginea indica (Bulbs Family: Liliaceae, Urginea)
21) Zingiber officinale (Rhizome, Family: Zingiberaceae, Ginger, Adrak)
22) Carica papaya (Leaves, Family: Caricaceae, Papita)
23) Withania somnifera (Root, Family: Solanaceae, Ashwagandha)
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24) *Terminalia belerica* (fruit, Family: Combretaceae, Bahera)

**Hypocholestremics**

1) *Allium cepa* (Bulbs, Family: Liliaceae, Onion)
2) *Acorus calamus* (Rhizome, Family: Araceae, Calamus, Bhadra)
3) *Allium Sativum* (Bulbs, Family: Liliaceae, Garlic)
4) *Commiphora mukul* (Gum resin, Family: Buceraceae, Gugglu)
5) Coffee and Tea
6) *Cyanopsis tetragonoloba* (Fruit Gum; Family: Leguminosae, Guar gum)
7) *Aloe barbadensis* (Gum, Family: Liliaceae, Aloes)
8) *Inula racemosa* (Root, Family: Convolvulaceae Pushkar)
9) *Medicago sativa* (Seeds, Family: Leguminosae, Alfa Alfa)
10) *Oryza Sativa* (Beans, Family: Gramineae, Rice bran)
11) *Pterocarpus marsupium* (wood, Family: Leguminosae, Bijsar, Pitasara)
12) *Olea europaea* (Leaves, Family: Oleaceae, Olive tree leaf)
13) *Trigonella foenumgracum* (Seed, Family: Leguminosae, Methidana)
14) *Triticum Sativum* (Family: Gramineae, Wheat Germ)
15) *Strychnos potatorium* (Seeds, Family: Loganiaceae, Kataka)
16) Capparis decidua (Fruit, Family: Capparaceae, caper, karir)
17) *Zingiber officinale* (Rhizome, Family: Zingiberaceae, Ginger)
18) *Emblica officinalis* (Fruit, Family: Euphorbiaceae, Amla, Amlaki)

**Diuretics**

1) *Boerhavia diffusa/repons* (Root, Family: Nyctaginaceae, Punarnava)
2) *Cocos nucifera* (Water of unripe fruit, Family: Palmae, Coconut water)
3) *Crataeva nurvala* (Bark, Family: Capparidaceae, Varuna)
4) *Cucurbita maxima/pepo* (Seeds, Family: Cucurbitaceae, Pumkin seeds)
5) *Cucumis sativa* (Seeds, Family: Cucurbitaceae, Cucumber seeds)
6) *Dalichos biflorus* (Seeds, Family: Leguminosae, Kulthi)
7) *Phyllanthus niruri* (Family: Euphorbiaceae)
8) *Portulaca oleracea* (Herb, Family: Portulaceae, Kulfa)
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9) Smilax Spp. (Root, Family: Liliaceae, Sarsaparlla)
10) Tribulus terrestris (Fruit, Family: Zygophyllaceae, Gokhru)
11) Tinospora cardifolia (Stems, Family: Menispermaceae, Guduchi)
12) Mimosa pudica (Root, Family: Leguminosae, Lajwanti)
13) Toddalia asiatica (Family: Rutaceae, Kanj)
14) Cucumis trigonus (Seeds, Family: Cucurbitaceae, pseudo-colocynth)
15) Urginea indica (Bulbs, Family: Liliaceae, Urginea)
16) Urtica dioica (Leaf, Family: Urticaceae, Bichu)
17) Zea mays (Hair, family Gramineae, Maiz Silk)
18) Zingiber officinale (Rhizome, Family: Zingiberaceae, Ginger)

Potassium Supplements

Portulaca oleracea (Herb, Family: Portulaceae, Kulfa)

Anticoagulants and Anti-thrombotics

1) Adhatoda vasica (Leaf, Family: Acanthaceae, Vasaka)
2) Allium sativum (Bulbs, Family: Liliaceae, Garlic)
3) Azadirachta indica (Leaf, Family: Meliaceae, Neem)
4) Ferula asafoetida (Gum resin, Family: Umbelliferae, Asafoetia)
5) Camellia Sinensis (Green tea, Family: Theaceae)
6) Curcuma longa (Rhizome, Family: Zingiberaceae, Turmeric)
7) Citrus flavanoids (Family: Rutaceae)
8) Luffa cylindrica (Seed, Family: Cucurbitaceae, Rajakoshtaki)
9) Plumbagin from plumbago (Family: Plumbaginaceae, Chitrak root)
10) Prunus domestica (Seed, Family: Rosaceae, Alubokhara)
11) Rheum Spp. (Root, Family: Polygonaceae, Rhubarb)
12) Solasodine from Solonum spp. (Family: Solanaceae)
13) Monomnonium Glycyrrhizinate from Glycyrrhiza spp. (Root, Family: Legumbiosae).
14) Zingiber officinale (Family: Zingiberaceae, Adrak, Ginger)

Cardiac Activity and Formulation Evaluation of Isolated Constituents of Piper longum linn
# Table 1.4 Plants studied clinically

<table>
<thead>
<tr>
<th>Plant</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aegle marmelos</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>Allium cepa</td>
<td>Shigellosis</td>
</tr>
<tr>
<td>Aloe barbendensis</td>
<td>Colic</td>
</tr>
<tr>
<td>Andrographis paniculata</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Areca catechu</td>
<td>Postoperative blood loss, bacteriuria</td>
</tr>
<tr>
<td>Artemisia vulgaris</td>
<td>Gallbladder calculus</td>
</tr>
<tr>
<td>Asparagus racemosus</td>
<td>Antidiabetic</td>
</tr>
<tr>
<td>Azadirachta indica</td>
<td>Burn wounds</td>
</tr>
<tr>
<td>Bactoca monieri</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Bocchusia diffusa</td>
<td>Common cold (2×)</td>
</tr>
<tr>
<td>Boswellia serrata</td>
<td>Fever, sore throat</td>
</tr>
<tr>
<td>Capsicum annuum</td>
<td>Hepato-cellular jaundice</td>
</tr>
<tr>
<td>Cedrus deodara</td>
<td>Symptomatic bladder disease</td>
</tr>
<tr>
<td>Cocos nucifera</td>
<td>Stomach carcinoma</td>
</tr>
<tr>
<td>Cyperus rotundus</td>
<td>Antidiabetic</td>
</tr>
<tr>
<td>Daucus carota</td>
<td>Burn wounds</td>
</tr>
<tr>
<td>Delucus biflorus</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Emblica officinalis</td>
<td>Worm infestation, <em>Ascaris lumbricoides</em></td>
</tr>
<tr>
<td>Eugenia jambolana</td>
<td>Decreases in mean blood sugar values</td>
</tr>
<tr>
<td>Foeniculum vulgare</td>
<td>Chronic nonspecific colitis</td>
</tr>
</tbody>
</table>

Cardiac Activity and Formulation Evaluation of Isolated Constituents of *Piper longum* linn
<table>
<thead>
<tr>
<th>Plant</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycyrrhiza glabra</td>
<td>Acne vulgaris, Chronic duodenal ulcers (2X), Chronic hepatitis, Hyperkalemia in Diabetes mellitus</td>
</tr>
<tr>
<td>Gossypium herbaceum</td>
<td>Male antifertility (3X)</td>
</tr>
<tr>
<td>Gymnema sylvestre</td>
<td>Mean blood sugar values (decrease) (2X), Serum lipids (decrease), Sweetness perception (decrease)</td>
</tr>
<tr>
<td>Holarrheita antidysenterica</td>
<td>Facial acne</td>
</tr>
<tr>
<td>Hydrocotyle asiatica</td>
<td>Shigellosis</td>
</tr>
<tr>
<td>Linum usitatissimum</td>
<td>N-3 fatty acids (increase)</td>
</tr>
<tr>
<td>Mallotus philippensis</td>
<td>Worm infestations, Ascaris lumbricoides</td>
</tr>
<tr>
<td>Morinda officinalis</td>
<td>Perceived pain relief, accelerated expulsion of worms</td>
</tr>
<tr>
<td>Mucuna pruriens</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Myristica fagrans</td>
<td>Calculi in kidneys and urinary bladder</td>
</tr>
<tr>
<td>Nardostachys jatamansi</td>
<td>Facial acne</td>
</tr>
<tr>
<td>Nelumbo nucifera</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Ocimum sanctum</td>
<td>Non-insulin dependent Diabetes mellitus</td>
</tr>
<tr>
<td>Oriza sativa</td>
<td>Oral rehydration therapy</td>
</tr>
<tr>
<td>Ptelea foetida</td>
<td>Shigellosis</td>
</tr>
<tr>
<td>Pueraria montanae-serrulata</td>
<td>Vitamin A/β-carotene content</td>
</tr>
<tr>
<td>Piper longum</td>
<td>Bioavailability of certain drugs (increase)</td>
</tr>
<tr>
<td>Piper nigrum</td>
<td>Disappearance of Giardia lambia</td>
</tr>
<tr>
<td>Plukenetia tuberosa</td>
<td>No damage to human gastric mucosa</td>
</tr>
<tr>
<td>Raphanus sativus</td>
<td>Migraine headaches</td>
</tr>
<tr>
<td>Rheum emodi</td>
<td>No adverse effects to metabolic parameters</td>
</tr>
<tr>
<td>Ricinus communis</td>
<td>Prevent chronic renal failure</td>
</tr>
<tr>
<td>Rubia cordifolia</td>
<td>Binding of healthy oral mucosa</td>
</tr>
<tr>
<td>Salix officinalis</td>
<td>Cardiac function</td>
</tr>
<tr>
<td>Santalum album</td>
<td>Peridontal disease</td>
</tr>
<tr>
<td>Saussurea lappa</td>
<td>Facial acne</td>
</tr>
<tr>
<td>Sesamum indicum</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Strychnos nux-vomica</td>
<td>Reduced frequency of angina</td>
</tr>
<tr>
<td>Teosinte chihua</td>
<td>Warts</td>
</tr>
<tr>
<td>Tamarindus indica</td>
<td>Nonketotic hyperglycemia</td>
</tr>
<tr>
<td>Tinospora cordifolia</td>
<td>Decrease in mean blood sugar values</td>
</tr>
<tr>
<td>Terminalis arjuna</td>
<td>Bioavailability of drugs (increase) (2X)</td>
</tr>
<tr>
<td>Tinospora cordifolia</td>
<td>Decrease in mean blood sugar values</td>
</tr>
<tr>
<td>Tinospora serrulata</td>
<td>Severe refractory heart failure</td>
</tr>
<tr>
<td>Terminalis bellirica</td>
<td>Stable angina pectoris</td>
</tr>
<tr>
<td>Terminalis chebula</td>
<td>Acne vulgaris</td>
</tr>
<tr>
<td>Terminalis chebula</td>
<td>Acne vulgaris</td>
</tr>
<tr>
<td>Tinospora cordifolia</td>
<td>Congestive cardiac failure</td>
</tr>
<tr>
<td>Tinospora serrulata</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Trilobis terrestris</td>
<td>Management of obstructive jaundice</td>
</tr>
<tr>
<td>Trigonella foemum-gracum</td>
<td>Calculi on kidney or urinary bladder, Congestive heart failure, Management of obstructive jaundice</td>
</tr>
<tr>
<td>Trinillia terrestris</td>
<td>Remission of angina pectoris</td>
</tr>
<tr>
<td>Urtica dioica</td>
<td>Total cholesterol, LDL, VLDL, triglycerides (decrease)</td>
</tr>
<tr>
<td>Valeriana jatamansi</td>
<td>Infantile rotavirus enteritis</td>
</tr>
<tr>
<td>Withania somnifera</td>
<td>Mild hypnotic action, Mild insomnia, decrease sleep latency, Sleep quality</td>
</tr>
<tr>
<td>Withania somnifera</td>
<td>Calcin on kidney and urinary bladder, Osteoarthritis, Psychomotor performance, Rheumatoid arthritis</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein cholesterol.
Heart diseases have been spread throughout the world. In the developing countries, major portion of budget is spent on the health care system. The serious diseases like heart diseases are badly affecting the health system of such countries. In the developing countries, major portion of the budget is spent on the health care sector. With the advancement of technology, life expectancy is continuously increasing. However, to fight against heart diseases, modern technology and new drugs are not still sufficient. Due to the cost factor involved in research and development of new drug molecules, the therapeutic treatment is becoming more and more costly. The cost, side effect and efficacy of new modern drugs makes the modern therapy heart diseases difficult to be accepted by a large group of people. Ayurveda has offered a novel remedies for the management of heart diseases. The plants such as arjuna, garlic, cinnamon and their formulations are very useful in treating heart diseases successfully. Guggula and pushkarmula has been shown to be a best combination for the treatment of ischemic heart diseases. Chandraprabha and Abana formulations are helpful in lowering the cholesterol levels. The detail phytochemistry of the plant which has explored new molecules for the treatment of heart disease. However, a lot of work is still required to find out the specific molecules which are responsible for their beneficial actions in heart diseases. The toxicological studies are also should be carried out in detail to find the exact efficacy of the plants. The detail investigation of the plants and their constituents for their pharmacological actions will help in the development of new molecules for the treatment of heart diseases. There is a urgent need to focus an the research and development of the products which can be obtained by the medical plants.

1.11 CYCLODEXTRIN TO IMPROVE PHYSICOCHEMICAL PROPERTIES OF MOLECULES:
The complexation approach has been frequently used to improve the aqueous solubility, wettability, and bioavailability of various drugs. [104-126] Complexation has also been used to decrease the toxicity of drugs, or to modify some of their physicochemical features. In particular, cyclodextrins have been extensively used to enhance the oral bioavailability and stability of a great number of pharmaceuticals. *Piper longum linn* consist of Piperine as one of major constituent. It was decided to isolate piperine and carry out the formulation development for the piperine. As piperine is having low water solubility, complexation can improve the solubility as well as other physicochemical parameters.

**History**
Cyclodextrins, also known as Schardinger dextrins, cycloamyloses, and cycloglucosamyloses, comprise a family of cyclic oligosaccharides obtained from starch by enzymatic degradation. They were discovered in 1891 by Villiers,' but the
first detailed description of the preparation and isolation was made in 1903 by Schardinger. Up to now α, β, γ and δ cyclodextrins, which are comprised of six, seven, eight, and nine glucose units, respectively, have been isolated by selective precipitation with appropriate organic compound. Cyclodextrins with 10-13 glucose units were also identified by chromatographic methods. Cyclodextrins composed of less than six glucose units are not known to exist due to steric hindrance and the 6-fold character of the starch helix.

By the end of the 1960s, the methods for the laboratory-scale preparation of cyclodextrins, their structure, physical and chemical properties, as well as their inclusion complex forming properties had been discovered. Summarizing the literature available at that time, the conclusions could be condensed into three points: (a) cyclodextrins are very interesting, promising molecules, worth further study, particularly because of their industrial possibilities. (b) cyclodextrins are very expensive substances, available only in small amounts as fine chemicals. (c) cyclodextrins are apparently highly toxic.

Investigations of cyclodextrin chemistry have been on the increase for several decades. The descriptions of the structure and properties of cyclodextrins and their applications have been the subject of several books, a number of review more than 800 patents, and innumerable papers. The reasons for the enormous effort in the study of cyclodextrins are that such molecules have inherent interest, that is, their physical and chemical properties merit study; they are the first and probably the most important example of relatively simple organic compounds which exhibit complex formation with other organic molecules; they are excellent models of enzymes which led to their use as catalysts, both in enzymatic and nonenzymatic reactions; and they are natural products and readily available for most researchers.

**Structures and Properties of Cyclodextrins**

Cyclodextrins comprise a family of three well known industrially produced major, and several rare, minor cyclic oligosaccharides. The three major cyclodextrins are crystalline, homogeneous, nonhygroscopic substances, which are torus-like macro-rings built up from glucopyranose units. The α-cyclodextrin (Schardinger’s α-dextrin, cyclomaltohexaose, cyclohexaglucan, cyclohexaamylose, α-CD, ACD, C6A) comprises six glucopyranose units, β-CD (Schardinger’s β-dextrin, cyclomaltoheptaose, cycloheptaglucan, cycloheptaamylose, β-CD, BCD, C7A) comprises seven such units, and γ-CD (Schardinger’s γ-dextrin, cyclomaltooctaose, cyclooctaglucan, cyclooctaamylose, γ-CD, GCD, C8A) comprises eight such units.

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Fig. 1.2 Structure of α, β and γ cyclodextrin.

α-cyclodextrin  β-cyclodextrin  γ-cyclodextrin

Fig. 1.3 Functional structural scheme of β cyclodextrin

Fig. 1.4 Molecular dimensions of cyclodextrins

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Figure 1.2 shows the chemical structures of α, β and γ cyclodextrins. As their appearance suggests, in the cyclodextrin molecules the glucose units, all in classical Cl chair conformation, are linked by α-1,4 bonds. This geometry gives the cyclodextrin the overall shape of a truncated cone with the wider side formed by the secondary 2- and 3-hydroxyl groups and the narrower side by the primary 6-hydroxyl (Fig. 1.3). The number of glucose units determines the dimension and size of the cavity (Fig. 1.4). The cavity is lined by the hydrogen atoms and the glycosidic oxygen bridges. The nonbonding electron pairs of the glycosidic oxygen bridges are directed toward the inside of the cavity, producing a high electron density and lending it some Lewis base character. As a result of this special arrangement of the functional groups in the cyclodextrin molecules, the cavity is relatively hydrophobic compared to water while the external faces are hydrophilic.

<table>
<thead>
<tr>
<th>characteristics</th>
<th>α</th>
<th>β</th>
<th>γ</th>
</tr>
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<tbody>
<tr>
<td>no. of glucose units</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>molecular weight</td>
<td>972</td>
<td>1135</td>
<td>1297</td>
</tr>
<tr>
<td>solubility in water (g/100 mL)</td>
<td>14.5</td>
<td>1.85</td>
<td>22.2</td>
</tr>
<tr>
<td>cavity diameter (Å)</td>
<td>4.7-5.3</td>
<td>6.0-6.5</td>
<td>7.5-8.3</td>
</tr>
<tr>
<td>height of torus (Å)</td>
<td>7.9 ± 0.1</td>
<td>7.9 ± 0.1</td>
<td>7.9 ± 0.1</td>
</tr>
<tr>
<td>pKₐ values</td>
<td>12.33</td>
<td>12.20</td>
<td>12.08</td>
</tr>
</tbody>
</table>

The most characteristic property of cyclodextrins is their remarkable ability to form inclusion complexes with a wide variety of guest molecules ranging from organic or inorganic compounds of neutral or ionic nature to noble gases. It seems that the only obvious requirement is that the guest molecules must fit into the cavity, even if only partially. Regardless of what kind of stabilizing forces is involved, the geometric capability and the polarity of guest molecules, the medium, and temperature are the most important factors for determining the stability of the inclusion complex. Geometric rather than the chemical factors are decisive in determining the kind of guest molecules which can penetrate into the cavity. If the guest is too small, it will easily pass in and out the cavity with little or no bonding at all. Complex formation with guest molecules significantly larger than the cavity may also be possible, but the complex is formed in such a way that only certain groups or side chains penetrate into the cyclodextrin cavity. In principle, inclusion complexes can be formed either in solution or in the crystalline state. However, complexation is usually performed in the presence of water. The stability strongly depends on the nature of the medium used for complexation. Although inclusion complex formation takes place in an organic solvent, the guest molecules are generally only weakly complexed. In general, the stability of an inclusion complex decreases with increasing temperature.
Derivatives of Cyclodextrins

Complexing ability can also be improved by chemically modifying the cyclodextrin molecules. Cyclodextrins can be modified by (i) substituting for the H atom of the primary or secondary hydroxyl groups, (ii) substituting for one or more primary and/or secondary hydroxyl groups, (iii) eliminating the hydrogen atoms of the \(-\text{CH}_2\text{OH}\) groups (e.g. by conversion to \(-\text{COOH}\)), or (iv) splitting one or more \(\text{C}2\text{-C}3\) bonds through a periodate oxidation. Recent interest in the use of chemically modified cyclodextrins for various purposes has generated a number of reviews dedicated to the syntheses and application of cyclodextrin derivatives. Intensive research is expected in the area of chemical and enzymic modification of CDs. Considering that CDs contain 18 (\(\alpha\)-CD), 21 (\(\beta\)-CD) or 24 (\(\gamma\)-CD) substitutable hydroxyl groups, the number of possible derivatives is unlimited. By 1997, the syntheses of more than 1500 derivatives have been published.

The known derivatives might be classified according to their substituents, their polarity, size, etc. For practical purposes they can be classified as follows: carriers (solubilizers, stabilizers) for biologically active substances; enzyme models; separating agents (for chromatography or batch processes); and catalysts and additives (as detergents, viscosity modifiers, etc.). The majority of the reported CD derivatives will never have any utilization because they involve complicated synthesis, resulting in expensive products. Even when they could be used for some of the above-mentioned purposes, the cost/benefit ratio precludes their production and utilization. An industrially produced and marketed CD derivative has to be produced by a simple, possibly “one-pot” reaction and must be nontoxic, when used as recommended; have an acceptable price; retain its complex forming capacity; and possess particularly advantageous properties for some specific application. Industrially, in ton amounts, the following CDs are actually produced: methylated CDs (RAMEB) randomly methylated \(\beta\) CD); hydroxyalkylated CDs (hydroxypropyl-\(\beta\) -CD and hydroxypropyl-\(\gamma\) -CD), acetylated CDs (acetyl-\(\gamma\) -CD); reactive CDs (chlorotriazinyl-\(\beta\) -CD); and branched CDs (glucosyl- and maltosyl-\(\beta\) -CD).

To elongate the actual CD cavity, substituents are attached to the primary or secondary side. This elongation may be hydrophilic in which case hydroxyalkyl groups are attached to the ring, or it might be hydrophobic. For example, substituting the primary hydroxyl groups with long fatty acid chains, “medusa” like molecules can be prepared. These molecules behave as detergents while retaining their complex-forming ability. The coming years will decide the utility of these derivatives. At present, mainly \(\beta\) and \(\gamma\) -CD, their hydroxypropylated derivatives, acetyl-\(\gamma\)-CD and also, in some specific cases, R-CD can be considered as drug carriers. Only hydroxypropyl-\(\beta\) -CD, sulfobutyl-\(\beta\) -CD, and \(\gamma\) -CD are supported by satisfactory toxicological documentation as parenteral drug carriers (in 1997). None of them is able to solve all of the solubility and stability problems in parenteral drug formulations. The development of 2-3 more such derivatives can be expected in the coming years.
Applications of Cyclodextrins

The actual or potential uses of CDs in pharmaceuticals, foods, cosmetics, chemical products and technologies. While a series of CD-containing products, or CD-using technologies is widely known in the food, cosmetic, and pharmaceutical industries, for the coming decade, significant new applications are expected from the use of CDs in environmental protection, in biotechnology, and in several industries, like the textile industry. As a result of complex formation, the characteristic properties of the included substance, such as solubility, chemical reactivity, pKa value, diffusion, electrochemical properties and spectral will be changed. This unique property has led to a widespread utilization of cyclodextrins in pharmaceutical, food, chemical and other industrial areas.

In the pharmaceutical industry, cyclodextrins and their derivatives have been used in drugs either for complexation or as auxiliary additives such as solubilizers, diluents, or tablet ingredients to improve the physical and chemical properties, or to enhance the bioavailability of poorly soluble drugs. In the food, cosmetics, toiletry, and tobacco industries, cyclodextrins have been widely used either for stabilization of flavors and fragrances or for the elimination of undesired tastes, microbiological contaminations, and other undesired. In the chemical industry, cyclodextrin and their derivatives are used as catalysts to improve the selectivity of reactions, as well as for the separation and purification of industrial-scale products. It has been reported that up to the end of 1986, about 750 patents were published relating to cyclodextrins and their applications, with an increase at the rate of 80 per annum. It is expected that
with increasing production, broadening research, and decreasing prices, the applications of cyclodextrins and their derivatives will rapidly increase in a wide variety of industries.

In recent years, cyclodextrins and their derivatives have also been used in various fields of analytical chemistry, especially in analytical separations. The applications in analytical field include in Spectrometric methods as UV-Visible, Analytical Luminescence, in NMR Spectroscopy, Electrochemical, Chromatographic Separations, Thin layer Chromatography, Affinity Chromatography, in Electrophoresis, in Gas Chromatography and in High-Performance liquid Chromatography. Cyclodextrins may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability. Cyclodextrin inclusion complexes have also been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material.

**CD Inclusion Complexes**

In an aqueous solution, the slightly apolar cyclodextrin cavity is occupied by water molecules which are energetically unfavored (polar-apolar interaction), and therefore can be readily substituted by appropriate “guest molecules” which are less polar than water. The dissolved cyclodextrin is the “host” molecule, and the “driving force” of the complex formation is the substitution of the high enthalpy water molecules by an appropriate “guest” molecule. One, two, or three cyclodextrin molecules contain one or more entrapped “guest” molecules. The hydroxy groups on the outer surface of the cyclodextrin molecule are able to form hydrogen bonds with other molecules and cyclodextrins can, like non-cyclic oligosaccharides and polysaccharides, form water soluble complexes with lipophilic water-insoluble compounds. Most frequently the host:guest ratio is 1:1. This is the essence of “molecular encapsulation”. This is the simplest and most frequent case. However 2:1, 1:2, 2:2, or even more complicated associations, and higher order equilibria exist, almost always simultaneously. The formed inclusion complexes can be isolated as stable crystalline substances. Upon dissolving these complexes, equilibrium is established between dissociated and associated species, and this is expressed by the complex stability constant $K_{1:1}$. The association of the CD and guest (D) molecules, and the dissociation of the formed CD/guest complex is governed by a thermodynamic equilibrium.

$$
CD + D \rightleftharpoons CD\cdot D
$$

$$
K_{1:1} = \frac{[CD\cdot D]}{[CD][D]} \quad \text{Eq.1}
$$

The most important primary consequences of the interaction between a poorly soluble guest and a CD in aqueous solution are as follows:
The concentration of the guest in the dissolved phase increases significantly, while the concentration of the dissolved CD-decreases. This latter point is not always true, however, because ionized guests, or hydrogen-bond establishing (e.g. phenolic) compounds may enhance the solubility of the CD.

The spectral properties of the guest are modified. For example, the chemical shifts of the anisotropically shielded atoms are modified in the NMR spectra. Also when achiral guests are inserted into the chiral CD cavity, they become optically active, and show strong induced cotton effects on the circular dichroism spectra. Sometimes the maximum of the UV spectra are shifted by several nm and fluorescence is very strongly improved, because the fluorescing molecule is transferred from the aqueous milieu into an apolar surrounding.

The reactivity of the included molecule is modified. In most cases the reactivity decreases, i.e., the guest is stabilized, but in many cases the CD behaves as an artificial enzyme, accelerating various reactions and modifying the reaction pathway.

The diffusion and volatility (in case of volatile substances) of the included guest decrease strongly.

The formerly hydrophobic guest, upon complexation, becomes hydrophilic; therefore its chromatographic mobility is also modified.

And in the solid state:

The complexed substance is molecularly dispersed in a carbohydrate matrix, forming a microcrystalline or amorphous powder, even with gaseous guest molecules.

The complexed substance is effectively protected against any type of reaction, except that with the CD hydroxyls, or reactions catalyzed by them.

Sublimation and volatility are reduced to a very low level.

The complex is hydrophilic, easily wettable, and rapidly soluble.

The complex formation of CDs with drugs such as antiplastic agents, antisense oligonucleotides, dihydroergotamine, psolaren, anticancer, and steroidal drugs has been recently reported. The formation of inclusion complexes with CDs enhanced the dissolution of indomethacin, increase their water solubility (e.g. itraconazole) decreased the ocular irritation of pilocarpine, modified the degradation of steroidal drugs in aqueous solution, to mask odor (garlic oil), flavor, to perform a drug release control (loteprednol),favor their absorption (e.g. piroxicam)and the stability of bioactive peptides. For local anesthetics, administration of dosage forms based on their CD inclusion complexes leads to slow release, thus prolonging anesthetic action and reducing cardiac and nervous system toxicity. Recent patent applications for
formulated products based on anesthetic/CD technology include those for the systems benzocaine-γ-CD (lozenge, topical cream) and propofol- sulfobutyl ether β-CD (pharmaceutically stable injectable dosage form).

**Industrial applications of cyclodextrins**

Until the late 1960s almost all cyclodextrin related chemistry was carried out in Europe but the obtained technological advances did not lead to notable industrial explorations of these oligosaccharides. However, in the early 1970s a number of industrial applications were being investigated, such as within the food and cosmetic industry. In the food industry, cyclodextrins were being investigated as stabilizers for flavoring agents and to reduce unpleasant odor and taste. In the cosmetic industry cyclodextrins were being tested as stabilizers of chemically labile compounds, to obtain prolonged action, to decrease local irritation and to reduce unpleasant odors. In Japan, there is a tradition for industrial usage of natural products and the Japanese regarded the parent cyclodextrins as natural materials originating from starch and thus as “non-toxic” natural products. By 1970, the Japanese were already actively studying the chemistry of cyclodextrins as well as their production and in the early 1980s cyclodextrins were introduced as industrial raw materials, mainly for the food and cosmetic industries. Within the next decade Japan became the largest cyclodextrin consumer in the world with an annual consumption of about 1800 tonnes, 80% of which went into the food industry and just over 10% into the cosmetic industry. Less than 5% were used in the pharmaceutical and agricultural industries. The industrial usage of cyclodextrins progresses somewhat slower in Europe and America. In the early 1990s, Procter & Gamble, an US based company, launched cyclodextrin based fabric softener with “longer lasting freshness” which was followed by couple of other cyclodextrin-based products and today the company is the largest single industrial user of cyclodextrins. Introduction of new excipients to the pharmaceutical industry is much more restricted than introduction of new excipients into toiletry and food products. However, in 1976 the world first pharmaceutical product, prostaglandin E2/β-cyclodextrin (Prostarmon ETM sublingual tablets), was marketed in Japan by Ono Pharmaceutical Co. It was not until about 12 years later that piroxicam/β cyclodextrin tablets were marketed in Italy by Chiesi Farmaceutici and the first cyclodextrincontaining formulation to be introduced to the US market was itraconazole/2-hydroxypropyl-β-cyclodextrin oral solution which was approved in 1997. Worldwide 30–40 different drugs are now marketed as cyclodextrin complexes (Table 1.6). In pharmaceutical formulations cyclodextrins are generally used as solubilizers but sometimes as stabilizers or to reduce local drug irritation.

**Cyclodextrins in dispersed systems**

Both the parent cyclodextrins and their derivatives have been used in dispersed vehicle systems such as emulsions, microcapsules, microspheres, nanospheres,
nanocapsules, liposomes and niosomes. Inclusion complexes of glycerides, fatty acids or fatty alcohols do possess surface activity and this property together with their ability to form aggregates frequently result in formation of dispersed systems. In other cases cyclodextrins have been used to increase drug loading of polymeric microspheres or to increase drug availability from dispersed systems. Novel surface active cyclodextrin derivatives have also been synthesized and used as drug delivery systems.

**Regulatory Status and Patents**

The regulatory status of CDs is continuously evolving. The natural cyclodextrin can be found in a number of pharmaceutical formulations in numerous countries throughout the world. Under certain conditions it is generally recognized as safe (GRAS) by the FDA and is listed in both the European Pharmacopoeia (Ph.Eur.) and US Pharmacopoeia (USP/NF) as well as in the Japanese Pharmaceutical Codex (JPC). In fact, all three natural cyclodextrins (i.e. α, β and γ cyclodextrin) are listed in JPC and in Japan all three have been approved as food additives. α -Cyclodextrin is listed in Ph.Eur. and 2-hydroxypropyl- β -cyclodextrin is listed in both Ph.Eur. and USP/NF. 2-Hydroxypropyl- β -cyclodextrin is cited in the FDA's list of Inactive Pharmaceutical Ingredients. Consensus appears to be building among regulators that cyclodextrins are excipients and not part of the drug substance, which is logical based on their physicochemical properties as drug solubilizers and stabilizers.

The first cyclodextrin-related patent entitled “Verfahren zur Herstellung von Einschlu verbindungen physiologisch wirksamer organischer Verbindungen” was issued in Germany in 1953. This patent describes the basic properties of α , β and γ cyclodextrin complexes, their precipitation in aqueous solutions and how the complexation enhances the chemical stability of biologically active compounds, increases their duration of activity and improves their taste. Current cyclodextrin patents fall into four categories. First, certain methods for production of cyclodextrins are patent protected.

For example, the cyclodextrin producing companies have patents on certain production techniques for producing α , β and γ cyclodextrin and some of their derivatives. Second, there are patents on pharmaceutical applications of certain cyclodextrin derivatives. For example, Johnson & Johnson has patent on pharmaceutical applications of 2-hydroxypropyl- β -cyclodextrin in the US and CyDex has a patent on sulfobutylether β -cyclodextrin. Third, there are patents on methods to improve the performance of cyclodextrins. For example, certain formulation techniques for improving the solubilizing effects of cyclodextrins through addition of hydroxyacids or water-soluble polymers. Finally, there are patents on specific drug/cyclodextrin combinations. More than third of all cyclodextrin-related patents fall into this last category.
Table 1.6 Pharmaceutical products using cyclodextrin

<table>
<thead>
<tr>
<th>Cytodextrin-containing pharmaceutical products</th>
<th>Trade name</th>
<th>Formulation</th>
<th>Country</th>
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<tbody>
<tr>
<td>α-Cyclodextrin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apracetil (PGE)</td>
<td>Prazosnin, Rigotter</td>
<td>I.V. solution</td>
<td>Japan, Europe, USA</td>
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<td>OP-1206</td>
<td>Opolin</td>
<td>Tablet</td>
<td>Japan</td>
</tr>
<tr>
<td>Cefditoren sodium HCl</td>
<td>Paosporn T</td>
<td>Tablet</td>
<td>Japan</td>
</tr>
<tr>
<td>β-Cyclodextrin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bravetox HCl</td>
<td>Ulgut, Loge,</td>
<td>Capsule</td>
<td>Japan</td>
</tr>
<tr>
<td>Cephalosporin (ME 1207)</td>
<td>Metax</td>
<td>Tablet</td>
<td>Japan</td>
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<tr>
<td>Chloroquine polvoide</td>
<td>Transilium</td>
<td>Tablet</td>
<td>Argentina</td>
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<td>Dexamethasone</td>
<td>Glyclysone</td>
<td>Ointment</td>
<td>Japan</td>
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<td>Diphenhydramin HCl, Chlorpromazine</td>
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<td>Chewing tablet</td>
<td>Europe</td>
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<td>Iodine</td>
<td>Mezo-Gargo</td>
<td>Solution</td>
<td>Japan</td>
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<td>Nicon, Niconam</td>
<td>Sublingual tablet, chewing gum</td>
<td>Europe</td>
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<tr>
<td>Nitroglycerin</td>
<td>Ninoex</td>
<td>Tablet</td>
<td>Europe</td>
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<td>Nitroprusside</td>
<td>Nitropen</td>
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<td>Onbeta</td>
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<td>PCG2</td>
<td>Prostamet E</td>
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<td>Prazoxin</td>
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<td>Tiraopin acid</td>
<td>Surynglyl</td>
<td>Tablet</td>
<td>Europe</td>
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<tr>
<td>2-Hydroxypropyl-β-cyclodextrin</td>
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<td></td>
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<tr>
<td>Caproseide</td>
<td>Proposial</td>
<td>Suppository</td>
<td>Europe</td>
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<td>Imiconazole</td>
<td>Spirinace</td>
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<td>Europe, USA</td>
</tr>
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<td>Mitomycin</td>
<td>Mitocyprax</td>
<td>I.V. infusion</td>
<td>Europe, USA</td>
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<tr>
<td>Methylated β-cyclodextrin</td>
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<td>Chlorpromazine</td>
<td>Chlorcol</td>
<td>Eye drop solution</td>
<td>Europe</td>
</tr>
<tr>
<td>17β-Estradiol</td>
<td>Aerodiol</td>
<td>Nasal spray</td>
<td>Europe</td>
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<tr>
<td>Sulfobutylated β-cyclodextrin</td>
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<td></td>
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<td>Voriconazole</td>
<td>Viral</td>
<td>I.V. solution</td>
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<tr>
<td>Zafarinone monosulphate</td>
<td>Geodon, Zelkox</td>
<td>IM solution</td>
<td>Europe, USA</td>
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<tr>
<td>2-Hydroxypropyl-γ-cyclodextrin</td>
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<td>Didofloric sodium</td>
<td>Voluran</td>
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<td>Te-99 Tebarocaine</td>
<td>Cardiotec</td>
<td>I.V. solution</td>
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</table>
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