CHAPTER-1

1. INTRODUCTION

Top-selling drugs in the world market about one third position. It may be either natural products or their derivatives. Moreover, for their broad structural diversity herbal products are widely recognized in the pharmaceutical company.

Knowledge of medicines, use of medicinal plants in India is widely used by tribal. For thousand of years, Indian plants have been attracting attention of foreign countries. Peoples from countries like China, Cambodia and Indonesia used to come to universities of India like Takshila (700BC) and Nalanda (500 BC) to learn health science of India (Strohl 2005).

Drug discovery was revolutionized after isolation, clinical study and commercialization of Penicillin by Chain, Florey in the early 1940s. After the success of Penicillin, manufacturer and researcher got succeeds for collection and culture of erythromycin, vancomycin, streptomycin, chloramphenicol, chlortetracycline and cephalosporin C. Mechanism-based screening is important part of HTS (Butler 2004).

Medicinal plant history is old as human civilization. From different documents like Papyrus Ebers contain more than 800 formulae and 700 different drugs. Drugs like acacia, castor oil, fennels are mentioned along with reference.

1.1 NATURAL PRODUCT IN MEDICINE

Natural products are derived from plants. Some plants were found which had very dramatic effects on the body and some were found to cure certain diseases. The knowledge of the plants was passed on through the generation and thus man gathered considerable experience of drug which could be obtained from plant in his surroundings.
The medicine men often also priests and thus the actual knowledge in many cases became enmeshed in a veil of myth and magic. This process can still be observed in the developing countries and the oldest information about plant used as drug originates from Sumerians and Akkadians (3rd millennium BC).

The Egyptians had extensive knowledge of technique of embalming, derived from their knowledge of plants. The famous Ebers papyrus, which dates from about 1550 BC, present a large number of crude drugs that are still of greater importance, such as castor seeds and gum Arabic.

Many authors of antiquity describe plant animals that could be used as drug. Among them were Hippocartes (ca.460-377 BC): The father of medicine. Theophrastus (372-87 BC), Pliny the Elder (AD 23-79), Dioscorides (AD ca.40-90), and Galenos (AD 129-199). Around AD 77 Dioscorides wrote Perihyales iatrikes in which he described more than 600 medicinal plants.

During the 16th and 17th centuries, the era of European exploration overseas, many new crude drugs were brought to Europe e.g. coffee, tea, coca seeds, Ipecacuanha root and Cinchona bark (Samuelsson 2004).

1.2 NP IN DRUG DISCOVERY

In the pharmaceutical industry the current trend in strategies for drug discovery is combinatorial chemistry combined with HTS techniques. HTS is today extremely efficient allowing screening of millions of sample per year.

Combinatorial libraries however will always be designed with ease and efficiency of synthesis in mind, so they are not likely to contain very complicated structures. Combinatorial chemistry has in fact been practiced by nature since time immemorial.

Secondary metabolites are produced by or organism to cope with the challenges of their; local environments and to gain advantage in the competition for living space and nutrients.
Mutations and recombination of the existing genetic material may give rise to new of modified enzymatic machineries, which may, in the course of evolution and under selective pressures, become fixed and inherited in a group of organisms. This has resulted in development of extremely complex chemical structure much richer in stereochemistry.

Although there is no doubt that many efficient new drugs will emanate from the current research trend, natural products will continue to be of importance for discovering leads for developments of drug, and in particular when complex enzymatic manipulations are required.

This is also realized by many pharmaceutical companies which start unit of research on natural product applying their resources for high-throughput screening to extract plants and other organisms as well as to fermentation broths and extracts of tissue and cell cultures (Samuelsson 2004).

1. Combinatorial biosynthesis

Elucidation of the biosynthetic pathways for natural products has now in several cases progressed to isolation and characterization of the enzymes involved and even to the recognition and cloning of the genes which code for these enzymes.

This opens up new avenues for the discovery of bioactive molecules as in the case of some polypeptides, e.g. the macrolides (Samuelsson 2004).

2. Ethnopharmacology

By using traditional remedies new drugs can also discovered with the help of research programme. It is termed as Ethnopharmacology and can be applied both to so called herbal remedies and products used by traditional healers (e.g. medicine man or shamans) in developing countries.
1.3 TRADITIONAL AND ALTERNATIVE MEDICINES

1. **Traditional Chinese system of medicine and kampoh system** (Mukherjee 2001)

   The Chinese system of medicine is still prevalent. According to this system, disease conditions are the expression of imbalance in *Yin and Yang like* excess or deficiency of either of them.

   For example, shivering occurs due to excess of *Yin* while excess of *Yang* causes fever. The treatment makes use of various herbs especially formulations. The important herbs from this system are *Ephedra sinica*, *Rheum palmatum*, *Panax ginseng*, *Schizonepta tenuifolia*.

2. **Ayurveda – Indian system of medicine** (Mukherjee 2001)

   Ayurveda is oldest written medical system in some pathological condition it is more effective than modern medicine. Ayurveda concept have been developed between 2500 to 500 BC in India. Established in 900 BC.

   Literally Ayurveda is called science of life, according to Indian Hindu mythology there are four Veda written by Aryan:
   - Rig Veda,
   - Yaur Veda,
   - Sham Veda,
   - Atharba Veda.

   It is believe that Ayurveda is an upaveda of Atharva Veda.

   Acc. to Ayu., disease can originate from the body and/or the mind due to external and internal factors. Ayurvedic medicinal preparations include complex mixture including plant and animal derived products of mineral and materials. Almost all the ancient text on Ayurveda divided medicinal knowledge into eight sections (Astanga). Ayurveda gain through experiences.
3. **Unani System of medicine** (Mukherjee 2001)

Persian introduced Unani Tibb to India was basis of Unani medicine is humoral theory which originate from Greece. Presence of four humours in the body is described by this theory – blood, phlegm, yellow bile and black bile.

Al Razi (850–923AD) was a popular physician of Unani Tibb. He devoted himself in clinical research. His observations were collected after his death, His book; in 1486 his book *Al-Hawi* was translated into Latin and published in Venice in 1547AD. He was the first person to describe treaties of smallpox and measles, *Al-Hasaba-Wa-Al-Judri*, is considered as collection of Unani Tibb.

4. **Homeopathic system of medicine** (Kokate et al. 2010)

In comparison to other system of medicine, Homeopathy is a newer one and has been developed in the eighteen century by Samuel Hahnemann German physician and chemist. He proposed that causes of disease can itself be used for its treatment. He put forth the laws like cure like, with this principle, he showed that cinchona produce the symptoms of malaria. He used different plant, minerals and animals and compiled in *Organon of Medicine*.

5. **Siddha system of medicine** (Kokate et al.2010)

The term 'Siddha 'means achievement and 'Siddhars' were saintly personalities, who attained proficiency in medicine through practice of Bhakti and Yoga.

According to traditional belief Lord Shiva unfolded the knowledge of medicine to his wife Parvati which was than pass to Siddhars. Like Ayurveda, this system belief on three humors i.e. Vatta, Pitta and Kapha and that all objects in universe are made up of five basic elements namely earth, water, sky, fire and air.
5. **Naturopathy and yoga** (Kokate et al. 2010)

Naturopathy is not merely a system of treatment but also a way of life which is based on way of nature. The attention is particularly paid to the eating and living habit, adoption of purificatory measures, use of hydrotherapy mud packs, bath, massage etc.

The system of Yoga is old as Ayurveda. The eight components of Yoga are restraint, observance of austerity, physical postures, restraining of sense organ, breathing exercise, contemplation, meditation and Samadhi.

7. **Bach flower remedies** (Kokate et al. 2010)

Bach flower remedies were discovered by Edward Bach, a physician in the early decade of twentieth century. These include 38 remedies are prepared from flowers of wild plant, bushes or trees. The remedies are prescribed as per the patient’s state of mind as, depression, anger, fear, worry, etc. The prescription is meant for achieving vitality and harmonious state of mind, the lack of which causes sickness.

8. **Aromatic Therapy** (Kokate et al. 2010)

It is one of most ancient healing arts and traces its origin to 4500BC, when Egyptian used aromatic substances in medicines. Greeks also used plant essences for aroma bath and scented massage. Prof. Gantle Fose, a French cosmetic chemist coined the term ‘Aromatherapy’ as described healing properties of essential oils.
1.4.1 INTRODUCTION

Diabetes mellitus is known from ancient time period. Historical accounts reveal that as early as 700-200 B.C. The term “Madhumeha” for diabetes was used by Sushruta mellitus in 6th Century. He describes it as a disease of rich, produced by over consumption of rice, flour and sugar (Alikhan et al. 2007).

By definition, the term diabetes is a disorder of impairment of metabolism due to impaired in secretion and/or resistant of insulin (WHO 2011).

Now a day for treatment of diabetes synthetic drugs or insulin is used. However the drugs are having considerable side effects, such as hypoglycemic condition, resistance and increase body weight. So it need for searching anti diabetic drug from nature with fewer side effects. Looking the active component from traditional drugs.

1.4.2. PREVALANCE

Diabetes has been identified as a lifestyle disorder that is estimated to afflict over 300 million by 2025. India is also plagued by the condition and it is expected that country will have over 50 million cases by 2025 (Wild 2004).
Figure: 1. PREVALENCE OF DM IN INDIA
EFFECT OF DM ON LIPID PROFILE AND OTHER BODY PHYSIOLOGY

1.4.3. FACTORS RESPONSIBLE FOR SUSCEPTIBILITY TOWARDS DIABETES (Jarald 2008).

1. Genetic susceptibility

It has been observed that in identical twins that if one twin has type I Diabetes mellitus, there is about 50% chance to second twin developing it but not all. This means that some additional modifying factors are about half the cases with genetic predisposition to type I. Diabetes mellitus have the susceptibility gene located in the HLA region of chromosome 6 (MHC class II region), particularly HLA DR3, HLA DR4, HLA DQ locus. For type-II diabetes multi-factorial inheritance is the most important factor in development. There are also 80% chances of developing diabetes in the other identical twin if one twin has the disease.
2. Auto immune factor

a. Presence of islet cell antibodies against GAD (glutamic acid decarboxylase), insulin etc.

b. Occurrence of lymphocytic infiltrate in around the pancreatic islets termed insulitis. It chiefly consists of CD$^+$ T lymphocytes with variable number of CD$^+$ T lymphocytes and macrophages.

c. Selective destruction of $\beta$-cells while other islet or polypeptide form of PP cells remain unaffected this is mediated by T-cell mediated cytotoxicity or by apoptosis.

3. Environmental factor

For type I diabetes it appear that certain viral and dietary protein share antigenic properties with human cell surface protein and trigger the immune attack on $\beta$-cells by the process of molecular mimicry factors include.

a. Certain viral infections preceding then onset of disease e.g. mumps measles, coxsackie -B virus, cytomegalo virus and infectious mononucleosis.

b. Experimental induction of type I DM with certain chemicals has been possible e.g. Streptozotocin and alloxan.

For type II diabetes certain environmental factor such as obesity, hypertension, and level of physical activity play an important role and modulate phenotyping of the disease.

4. Insulin resistance and impaired secretion

For type II diabetes mellitus most prominent feature is the lack of responsiveness of peripheral tissue to insulin, especially skeletal muscle and liver. $\beta$-Cell also secretes inadequate insulin. Increased hepatic glucose synthesis: Insulin helps in storage of glucose in liver in form of glycogen and suppresses gluconeogenesis.
5. Rapid urbanization

Urbanization has brought about marked variation in the living condition. Socioeconomic development over the last 40-50 years has resulted in dramatic changes in the lifestyle from traditional to modern.

This has resulted in physical activity due to technological advancement where most of the manual work has been supplemented by modern gadgets.

6. Ageing population

As we grow old, biochemical changes that occur in our body such as: loss of glucose tolerance, which is characterized by after meal there is elevation of blood glucose and insulin.

Figure: 2. EFFECT OF DM ON DIFFERENT BODY PHYSIOLOGY
1.4.4 TYPES OF DIABETES MELLITUS (Sharma et al., 2007)

1. Type-1 DM

It is IDDM. Insulin replacement therapy is required in type 1 diabetes for sustain life. Insulin can be administered by using a manual device or insulin pump which continuously supplies insulin. Interruption in insulin replacement therapy leads to keto-acidosis and which is life threatening.

2. Type-2 DM

It is NIDDM or “maturity onset diabetes”. It usually found in people who are over 40 and overweight. Diabetes arises not from lack of insulin but because their target cells have either insulin insensitive (peripheral resistance to insulin). Complications usually appear are:

Micro vasc. Complications:

- Retinopathy, Nephropathy, Neuropathy

Macro vasc. Complications:

- Atherosclerosis, Dyslipidemia, Neuropathy
3. Type-3 DM

In this type there are secondary causes of hyperglycemia e.g. chronic pancreatitis or chronic drug therapy with glucocorticoids, thiazide diuretics, diazoxide, and growth hormone or with some protease inhibitors used to treat human immunodeficiency virus infection.

4. Type-4 DM

In gestational diabetes mellitus (GDM), Glucose level abnormality for first time in pregnancy is called gestational diabetes mellitus. Placental hormone secreted during pregnancy is responsible for glucose resistance which is responsible for elevation in blood glucose level and prominent in last trimester of pregnancy. There is no genetic predisposition.
Figure: 3. Factors responsible for hyperglycemia

1. Increase gut and carbohydrate absorption
2. Insulin secretion
3. Increase glucagon secretion
4. Increase hepatic glucose production
5. Decrease peripheral glucose uptake
1.5. HERBAL DRUGS

21,000 plants have been listed by WHO, which are used all over the world. In India about 2500 species are found, 150 species are commercially used in large scale. Herbs regenerate β-cells which help to maintain glucose and also show hypolipidemic and antioxidant property (Jarald 2008).

Lead molecules of plant helps in development of conventional drugs. Development of metformin from Galega officinalis for treatment of diabetes. Preclinical and clinical trials on herbal drugs are required to prove their efficacy and safety (Seth 2004). Interestingly in most cases the antidiabetic property has been attributed to phytochemicals derived from these medicinal plants, most of the phytochemicals are antioxidants e.g. epicatechin, a polyphenols flavonoids.

The active principle of plant helps in β-cell regeneration, insulin secretion and increase sensitivity (Gymnema sylvestre, bitter melon and extract of Indian Kino tree). Medicinal plant have been reported to effect various metabolic enzyme involved in the diabetogenic (Fenugreek, Tinospora, Ivey guard and bitter melon) correcting the imbalance glucose metabolic disturbances, improving the glucose uptake, inhibiting gluconeogenic enzymes and modulating glycolitic and lipolitic pathways in diabetic conditions. In late complication of diabetes, it has been observed that medicinal plant (Bitter melon, Tinospora, Bilbery etc.) attenuate renal hypertrophy and ameliorate diabetic neuropathy and gastropathy.

Different types of phytoconstituents of plant like: alkaloids decrease glucose transport by inhibiting α-glucosidase, imidazoline compounds stimulate insulin secretion. Polysaccharides increases serum insulin level. Dietary fibers adsorb glucose. Flavonoids suppress the glucose level, improve lipid profile. Saponin and ferulic acid are insulin secretagogue (Bhusan 2010).
1.6 CHEMICAL METHODS FOR INDUCTION OF DIABETES

Chemical induced Type -1 diabetes is the most commonly used

- Specifically damage β-cell.
- Causes temporary inhibition of insulin production and secretion.
- Diminish the metabolic efficacy of insulin in target tissues.

In general, chemicals are the first category of interest they reproduce lesions resembling insulin dependent diabetes mellitus.

Alloxan- induced diabetes

Alloxan, a cyclic urea analog, was the first agent in this category, which was reported to produce permanent diabetes in animal.

Mechanism of action

The mechanism by which induces diabetes is not very clear. Alloxan is a highly reactive molecule that is readily reduces the diueric acid which is the auto-oxidized back to alloxan resulting in the production of free radicals. These free radicals damage the DNA of β-cells and cause of cell death. Second mechanism proposed for alloxan is its ability to react with protein–SH groups, especially the membrane proteins like glucokinase on the β-cells, finally resulting in cell necrosis. However there are major species differences in response to alloxan.

Streptozotocin- induced diabetes

Streptozotocin is a broad spectrum antibiotic.

Mechanism of causing β-cell damage

- By process of methylation.
- Free radical generation.
- Nitric oxide production.
STZ induced diabetes in almost all species of animals. Diabetogenic dose varies with
species, rats (50-60 mg/kg, i.p. or i.v.), mice (175-200 mg/kg i.p or i.v.) and dogs
(15mg/kg for 3 days). Blood glucose shows triphasic response as seen in alloxan
treated animals, with hyperglycemia at 1 h, followed by hypoglycemia, which last for
6h, and stable hyperglycemia by 24-28h after STZ administration.

Modification

Multiple low dose of STZ also induces diabetes by causing immune mediated
pancreatic insulitis in rats. It has also been shown to have diabetogenic effect on the
golden hamsters when given i.p. 50 mg/kg. Cyclosporine-A when given with STZ
enhances its diabetogenic efficacy. STZ combined with complete Freund's adjuvant,
*Mycobacterium butyricum* (components of CFA), *Listeria monocytogens*, or
endotoxin administered 24 h prior to STZ (25mg/kg) and then repeated in the three
subsequent weeks all produce hyperglycemia. Fasting for 48 h (24 hr prior to 24 hr
subsequent to the STZ injection) also produce hyperglycemia neither four
administrations neither of CFA nor of STZ alone result in persistent hyperglycemia.
### 1.7 Anti Diabetic Herbs

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Ayurvedic / common Name/</th>
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<tbody>
<tr>
<td>Annona squamosa</td>
<td>Hypoglycemic</td>
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<tr>
<td>Artemisia pallens</td>
<td>Hypoglycemic</td>
</tr>
<tr>
<td>Areca catechu</td>
<td>Hypoglycemic</td>
</tr>
<tr>
<td>Beta vulgaris</td>
<td>Increases glucose tolerance.</td>
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<tr>
<td>Boerhavia diffusa</td>
<td>Increase plasma insulin level,</td>
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<tr>
<td>Bombax ceiba</td>
<td>Hypoglycemic</td>
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<tr>
<td>Butea monosperma</td>
<td>Anti-hyperglycemic</td>
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<tr>
<td>Camellia sinensis</td>
<td>Anti-hyperglycemic activity</td>
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<tr>
<td>Capparis deciduas</td>
<td>Hypoglycemic</td>
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<tr>
<td>Caesalpinia bonducella</td>
<td>Insulin secretagogue</td>
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<td>Coccinia indica</td>
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<td>Emblica officinalis</td>
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<td>Eugenia uniflora</td>
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<tr>
<td>Enicostema littorale</td>
<td>Increase glucose metabolism</td>
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<tr>
<td>Ficus bengalensis</td>
<td>Hypoglycemic</td>
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<tr>
<td>Gymnema sylvestre</td>
<td>Anti-hyperglycemic</td>
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<tr>
<td>Hibiscus rosa-sinesis</td>
<td>Initiates insulin release</td>
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<tr>
<td>Ipomoea batatas</td>
<td>Reduces insulin resistance</td>
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<tr>
<td>Momordica cymbalaria</td>
<td>Hypoglycemic</td>
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<td>Herb</td>
<td>Effect</td>
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<td>-----------------------------</td>
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<td>Murraya koenigi</td>
<td>Hypoglycemic</td>
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<tr>
<td>Musa sapientum</td>
<td>Antihyperglycemic</td>
</tr>
<tr>
<td>Phaseolus vulgaris</td>
<td>Hypoglycemic</td>
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<tr>
<td>Punica granatum</td>
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<td>Salacia reticulate</td>
<td>$\alpha$-glucosidase inhibitor</td>
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<tr>
<td>Scoparia dulcis</td>
<td>Insulin-secretagogue</td>
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<tr>
<td>Swertia chirayita</td>
<td>Stimulates insulin release</td>
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<td>Syzygium alternifolium</td>
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<td>Terminalia belerica</td>
<td>Antibacterial, hypoglycemic</td>
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<td>Terminalia chebula</td>
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<tr>
<td>Tinospora crispa</td>
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<tr>
<td>Vinca rosea</td>
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</tr>
<tr>
<td>Withania somnifera</td>
<td>Hypoglycemic, diuretic and</td>
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*Table - 1 List of Antidiabetic herbs*
1.8 LIVER DISORDERS AND HERBAL DRUGS

INTRODUCTION

All over the world people depend on herbs for treatment of various ailments. About 80% of people primarily depend on herbs for their health care benefit. Ancient literature also revealed that ancient peoples used herbal drugs for treatment of various diseases like diabetic, immune, and liver disorders, Alzheimer’s disease. The herbal drug products are prepared from renewable resources of raw materials by eco-friendly processes and will bring economic prosperity of peoples (Kashw 2011).

Near about 160 constituents of 101 different plants possess hepatoprotective activity. In India > 87 plants have been used in herbal formulations. Till now in modern age we generally depend on herbal drug for treatment of liver disorders. No safer hepatoprotective drug available in modern medicine (Singh 2012).
1.8.1 DIFFERENT TYPES OF HEPATIC DISORDER

I. Hepatitis A

Hepatitis A is a RNA virus belonging to the genus hepatovirus of the Picornaviridae family.

Humans are the only known reservoir for the virus and transmission occurs primarily through the fecal oral route. HAV infection is usually acute, self-limiting, and confers lifelong immunity. Life cycle in the human host classically begins with ingestion of the virus.

Absorption in the stomach or small intestine allows entry into the circulation and uptake by the liver. Replication of the virus occurs within hepatocytes and gastrointestinal epithelial cells. New virus particles are released into the blood and secreted into bile by the liver. The virus is then either reabsorbed to continue its cycle
or excreted in the stool. The enterohepatic cycle will continue until interrupted by antibody neutralization (Mohan 2010).

2. Hepatitis B

It is a partially double-stranded, circular DNA with 3,200 base pairs that typically infects liver cells, although it has been found in kidney, pancreas, and mononuclear cells. Seven HBV genotypes exist (A to H).

Upon infection, replication of the virus begins by attachment of the virion to the hepatocyte cell surface receptors. The particles are transported to the nucleus where the DNA is converted into closed, circular DNA that serves as a template for pregenomic RNA.

Viral infection, the antibody response is strong. In an acute infection, however, the cytotoxic T-cell response is critical to viral clearance. If the response is weak, chronic infection is likely (Mohan 2010).

3. Hepatitis C

In the vast majority of cases, an acute HCV infection leads to chronic infection. The immune response in an acute HCV infection is mostly insufficient to eradicate the virus.

During the early phases of infection, natural killer cells are activated as HCV RNA levels rapidly raise. A combined effort of HCV specific CD4 and CD8 T lymphocytes and interferon co-expression decrease viral replication.

The eradication of HCV by cytotoxic T lymphocytes may occur either as a result of induced apoptosis by infected hepatocytes or by the release of interferon to stifle viral replication (Vasudevan et al.2005).
4. Hepatitis D

It is an “incomplete virus”, it can only replicate in the presence of Hepatitis B virus. It has a small single-stranded RNA genome. This genome is encapsulated within a protein coat of HBs Ag that allows the hepatitis D virus to gain cell entry. Transmission occurs via serous body fluids, contaminated needles, syringe and plasma products via sexual contact. Hepatitis D state department of health (Washington state department of health).

5. Hepatitis E

It is RNA virus of single-stranded. Primarily transmitted by fecal-oral route and contaminated drinking water. Suggested that it is likely a zoonotic infection transmitted from domestic animals like pigs wild animal species (Washington state department of health).

6. Hepatitis G

It is RNA virus of single-stranded. It can be identified by PCR amplification technique. It distinct from the foregoing hepatitis viruses has been designated separately as hepatitis G, HGV infection has been found in blood donors. Patients on haemodialysis and as confection HIV. HGV is cleared from plasma in majority of individuals while a small percentage of cases have chronic HGV infection that does not develop hepatitis (Mohan 2010).

7. Liver Cirrhosis (Mohan 2010)

It represents the irreversible and stage of several diffuse diseases causing hepatocellular injury and is characterized by the following features

1. It involves the entire liver.
2. The normal lobular architecture of hepatic parenchyma is disorganizing.
3 There is formation of nodules separated from one another by irregular band of fibrosis.

8. **Alcoholic liver cirrhosis** (Mohan 2010)

Alcohol liver disease is the term used to describe the spectrum of liver injury associated with acute and chronic alcoholism. There are three sequential stages in alcoholic liver disease.

Most common form of lesion constituting 60-70% of all cases of cirrhosis. Several terms have been used for this type of cirrhosis portal cirrhosis. Hobnail cirrhosis, Nutritional cirrhosis, diffuse cirrhosis and micro nodular cirrhosis and Alcohol cirrhosis is the most common form of lesion constituting 60-70% of all cases of cirrhosis.

9. **Hepatotoxicity**

Drugs and chemicals may potentiate liver disease. Fact any patient presenting with liver disease or unexplained jaundice is thoroughly questioned about history of drug intake or exposure to chemicals disease severity of hepatotoxicity is greatly increased if the drug is continued after symptoms develop (Mohan 2010).

**Example different drugs causes hepatotoxicity:**

- Carbontetrachloride, Acetaminophen
- Methyldopa, Tetracycline
- Halothane, Ketoconazole
- Nitrofurantoin, Isoniazid
- Vitamin-A
1.8.2 HERBAL DRUGS FOR MANAGEMENT OF HEPATIC DISORDERS

From ancient period of time we are depending on natural products and their derivatives for treatment of liver ailments (Sharma 2009). Transplantation of liver, shown limited therapeutic benefits in modern medicine. Modern drug also having less success in therapy. Therefore it need alternative approaches of treatment.

Unavailability of modern drug for treatment of liver plant drugs and products has been recommended. Silymarin as hepatoprotective, *Gentiana asclepiadea* L. stomachic and as hepatoprotective agents in traditional medicine, Gentiana species is distributed widely which contain gentiopicrin, swertiamarin also posses hepatoprotective activity D-galactosamine induced hepatotoxicity in rats. Gentiana genus contain relatively large amounts of xanthones is well known to exhibit antioxidant and posses hepatoprotective activity. *Trichosanthes cucumerina* is used in the treatment of hepatomegaly, hepatitis. *Pachanabheda churana* used for the treatment of liver ailments one of its important ingredient is *Trichosanthes cucumerina* (Sivarajan et al 1994).

1.9 FREE RADICALS AND ANTIOXIDANT

1.9.1 FREE RADICALS

Molecule or molecular species that contains one or more unpaired electrons and can independently exist (Vasudevan et al.2005).

1.9.2 DIFFERENT FREE RADICALS (Rangan et al.1993)

- $\text{O}_2^-$
- $\text{HO}_2$
- $\text{H}_2\text{O}_2$
- $\text{OH}^-$
1.9.3 ANTIOXIDANT

Antioxidants may be endogenous or exogenous in nature; it may block generation of oxidants, intercept any and neutralize the oxidant and block the chain propagation (Halliwell et al. 1998).

1.9.4 OXIDATIVE STRESS

“OS” occurs due to increase in oxidative metabolism. Different factors are responsible for oxidative stress such as: alcohol, drugs, accidents, excessive cold, infections, improper diet and toxins (Duckworth 2001).

1.9.5 OXIDATIVE STRESS IN DIABETES

All over the world peoples are suffering with diabetes, which is a chronic metabolic disorder. In which inadequacy of insulin secretion occur or response of insulin to its receptor decreases, which is identified by increase blood glucose level and abnormality in metabolism and utilization of carbohydrate, lipid,
and protein occur. This is responsible for macro and micro-vascular dysfunctions of body system (Satyanarayana et al 2011).

1.9.6. COMPLICATION OF DIABETES

Hyperglycemia may induce oxidative stress that plays a role in complication of DM.

1. CV Disease:
LDL oxidation is responsible for cardiovascular disease. It is responsible for atherogenesis due to LDL Oxidation.

2. D Nephropathy:
It is a major macrovascular complication because high glucose level is responsible hydrogen peroxide production and damage of nephron.

3. D Neuropathy
In diabetes hyperglycemia causes degeneration of neuron through increased oxidative stress induced by DM.

4. D Retinopathy
It another complication of diabetes. Activation of NF-kB is considered as important signaling pathway of endothelial cells apoptosis it is caused by high glucose levels.

5. E Dysfunction
It is commonly occur in young -aged diabetic patients.
Figure: 5. Free radicals and antioxidant
Introduction

Chapter 1

Figure: 6. Mechanism of antioxidant in DM

Figure: 7. Complication of diabetes and its association with oxidative stress
1.9.7 FREE RADICAL AND DISEASES (Vasudevan et al 2005).

i. *Cardiovascular disease CHD*:

Oxidized LDL, formed by the action of free radicals, promote atherosclerosis and CHD.

ii. *Cancer*:

Damage of DNA, mutation and cytotoxicity can caused by free radical and cause carcinogenesis and inhibit DNA repair and inactivate tumor suppressor gene.

iii. *Inflammatory disease*:

Rheumatoid arthritis is a chronic inflammatory disease. The free radicals produced by neutrophils are the predominant causative agent. Other inflammatory disorders- Chronic glomerulonephritis and ulcerative colitis is also due to ROS on extracellular components (e.g. collagen and hyaluronic acid)

iv. *Respiratory disease*:

Direct exposure of 100% oxygen to lungs for a longer period (>24 Hr) is known to destroy endothelium and causes lungs edema .This is mediated by free radicals.

v. *Diabetes*:

In insulin dependent DM pancreatic damage occurs due to accumulation of free radicals and leads to insulin dependent DM.

vi. *Cataract*:

Increased exposure to oxidative stress contributes to cataract formation, which is mostly related to aging.

vii. *Male infertility*:

Sperm motility and viability decreases by free radicals, and thus may cause male infertility.
viii. Aging process:

Free radicals are closely associated with the various biochemical and morphological changes that occur during normal aging.

ix. Other disease:

Free radicals play a key role in Parkinson's disease, multiple sclerosis, liver cirrhosis, muscular dystrophy, toxemia of pregnancy etc.
Mechanism of free radicals, antioxidant defence and oxidative stress.
**1.9.8. CLASSIFICATION OF ANTIOXIDANT ACCORDING TO THEIR NATURE AND ACTION** (Vasudevan et al 2005).

**A. ENZYMATIC ANTIOXIDANT**

*i) Superoxide dismutase:*
It converts superoxide to hydrogen $\text{H}_2\text{O}_2$ and $\text{O}_2$. The mitochondrial SOD is manganese dependent.

*ii) Catalase:*
Hydrogen peroxide produced by the superoxide dismutase, is metabolized by catalase.

$$\text{Catalase} \quad 2\text{H}_2\text{O}_2 \rightarrow \text{O}_2 + 2\text{H}_2\text{O}.$$

*iii) Glutathione reductase:*
It detoxifies $\text{H}_2\text{O}_2$ to $\text{H}_2\text{O}$ while reduced glutathione(G-SH) is converted to oxidized glutathione (GS-SG). The reduced glutathione can be regenerated by the enzyme glutathione reeducates utilizing NADPH.

**B. NON ENZYMATIC ANTIOXIDANT**

*a. Nutrient antioxidant:*
- Carotenoids ($\beta$-Carotene),
- $\alpha$-tocopherol,
- ascorbic acid,
- selenium.

*b. Metabolic antioxidant:*
- Glutathione
- Ceruloplasmin
• Albumin
• Bilirubin
• Transferrin
• Ferritin
• Uric acid.
Classifications of antioxidants
1.10. BACTERIAL INFECTIONS AND HERBAL DRUGS

1.10.1. INTRODUCTION

About 80% population of developing depends upon traditional medicines. According to World Health Organization (WHO) countries, generally plant drugs, for primary health care (WHO. Fact sheet N’13427). It has been estimated that 45, 000 plants are available in Indian; about 7500-8000 plants are used in traditional system, and only about 1500 plants in traditional formulations (Silva et al.2009).


In modern conventionally system antibiotic therapy used for bacterial infections(Mahesh et al2003). Antibiotics typically retard bacterial multiplications by entering the microbes and interfering. However, indiscriminate use of antimicrobial agents leads the evolution of bacteria toward resistance (Treadway 1998).

Now a day there is increasing evidence of drug resistance. For example multidrug resistant (MDR) *Staphylococcus aureus*, β-lactamase degrading penicillin and cephalosporin group of antibiotics derived antibiotics. Multidrug resistance of *Staphylococcus*, *Pseudomonas*, and *Escherichia* has been reported worldwide. Researchers are searching for new drug from natural resources (Dubey et al. 2012).

Plants have can synthesize different compounds like phenolic, nitrogen, vitamins and terpenoids and other metabolites these are serve as defence against microbes (Bharathi et al. 2011).
1.10.2. BACTERIA

Bacteria are the most abundant prokaryotic microorganism ever found throughout the world. These are regarded as the first life form appeared on the earth. Bacteriology is a branch of microbiology that deals with detailed study of bacteria. An approximation of $5 \times 10^{30}$ bacteria exists in this earth comprising the largest biomass above plants and animals (Whiteman et al., 1998). 5-10% of the total bacterial species, they cause life threatening diseases such as: cholera, tuberculosis, and gonorrhoea; whereas most of the bacteria are non-pathogenic in nature and beneficial for human beings in one way or other (Whitman et al. 1998).

1.10.3 HERBAL DRUGS FOR TREATMENT OF BACTERIAL INFECTIONS

Plant and plant product posses a led role in traditional medicine system, and in different communities of world, in different countries of Asia and Africa, 80% of populations use traditional medicine system for primary healthcare benefits. Ethnobotany is a branch of Ethnopharmacology. It deals with medicinal use of plants, study of bioactive chemical component from nature (Nash et al. 2011).
1.10.4 HERBAL DRUGS FROM NATURE

i. Flavonoids

It make complex with proteins of bacteria and with bacterial cell, membrane which is responsible for antibacterial properties (Fowler 2011).

ii. Terpenes

They contain additional element as oxygen and these are recently reviewed as antimicrobial compounds (Kurek et al. 2011).

iii. Phenolics & polyphenols

Largely found in plants, these are responsible for anti-oxidative as well as antimicrobial properties (Saleem et al 2010).

iv. Alkaloids

Alkaloids posses antimicrobial properties. Heterocyclic nitrogen compounds; these also protect plants from different microbial infections. Leaves extracts of Gymnema montanum and root bark extract of Tabernaemontana catharinensis shows antimicrobial properties (Ramkumar).

v. Coumarins

Coumarins posses’ antimicrobial properties coumarin, scopoletin, can use as anti TB drugs (Garcia 2012).
1.10.5. BACTERIA AND DIFFERENT PATHOLOGICAL STATE

1. **E. Coli**

It is a gm (–Ve) bacteria that normally live in the intestines of healthy people and animals, primarily cattle. The symptoms of infection are variable. Some body are asymptomatic. Others diarrhoea, vomiting and nausea.

2. **S. aureus**

Gram (+Ve) bacteria, with dm of 0.5 – 1.5 µm and characterized by indi. cocci, the Staphylococci are non-motile. *S aureus* is considered to be a major pathogen that and infects both hospitalised patients with lack of immunity, and healthy persons also. It also responsible for local infections.

3. **B. subtilis**:

It is relatively benign. It is not causes human disease and produces enzyme subtilin.

4. **P. aeruginosa**

*P. aeruginosa* is responsible for chronic infections in CF peoples. Chronic pulmonary infection with *P. aeruginosa* develops in most patients with CF;
Introduction

Chapter 1

E. coli

S. aureus
\textit{B. subtilis}

\textit{P aeruginosa}

\textbf{Figure: 8. Different Microbes}
1.1.1 PLANT INTRODUCTION

**Figure: 9 PLANT AND PLANT PARTS**

Plant: *Tamarindus indica*

Seeds: *T. indica* L.
Fruits and leaves of *T. indica*
Flowers and fruits of *T indica*
Figure 9. Structure of plant and plant parts: Fruits, seeds, leaves, flowers
1.11.1. BIOLOGICAL SOURCE (Kirtiakar et al. 2006)

**Botanical name:**

*Tamarindus indica* L.,

Family: Caesalpiniaceae

**Taxonomical classification**

- **Kingdom:** Plantae
- **Phylum:** Spermatophyte
- **Class:** Angiosperm
- **Sub class:** Dicotyledone
- **Genus:** *Tamarindus*
- **Species:** *indica*

1.11.2. VERNACULAR NAMES (Kirtiakar et al. 2006)

- **Assam:** Teteli
- **Bengal:** Ambli, Tentul, Tinturi, Nuli
- **English:** amarind tree
- **Gujarat:** Ambli, Aml
- **Hindi:** Imli, Aml,
- **Malayalam:** Amlam
- **Odiya:** Tentuli
- **Punjab:** Imli
- **Tamil:** Ambilam, Amilam
- **Telugu:** Amlika, Chinta, Sinja, Sinta
- **Urdu:** Imli
- **Nepal:** Titri
1.11.3. DESCRIPTION (Kirtiakar et al.2006)

_Tamarindus indica_ (Figure-12) is large, evergreen tree, 12-18 m. high in height, leaflets: subsessile, 10-20 pairs, tolerably closely set on the rachis, 8-30 by 5-8 mm. oblong, obtuse, glabrous reticulately veined.

Flowers: pale yellow or pinkish. Flowers: few flowered racemes at the end of the branchlets, pedicil 6-10 mm. long slender articulate below the calyx, glabrous, bracts concave, 6-8 mm. long, enclosing the buds. Cadcous; bracteoles small.

Calyx 1.3 cm. long ; tubes narrowly turbinate, 4 mm. long; segments 8 mm. long, sub equal oblong, some what oblique, obtuse or subacute.

Petals 3 (an upper and 2 lateral), 1 cm. long, sub equal obovate, oblong yellowish with pink strip. Stamens 3 fertile, connate nearly half their length; filament pubescent at the base; anther oblong.

Ovary stalked; 8-12 or more style pubescent, equalling stamens. Puds 7.5 -20 cm. long slightly curved, subcompressed, scurfy.

Seeds 3-12 obovate-oblong, truncate at the ends, 1.6 by 0.8 cm, compressed with shallow oblong pit on the each of the flat faces, smooth, brown shining.
1.11.4. PLANT INTRODUCTION

_Tamarindus indicia_ L., belongs to family: Caesalpiniaceae consists of 727 genera and 19,327 species (Kirtiakar et al.2006).

The tamarind (_Tamarindus indica_ L.) It is originating to tropical Africa. Also cultivated in subtropical China, India and Pakistan (Kirtiakar et al.2006).

For preparation of various dishes leaves and flowers can be used. Feed to draught animals. Tannins are present in leaves and bark. Red dye can be obtained from leaves. Leaves contain vitamin C and ß-carotene and also high mineral contents like K, P, Ca, and Mg (Kirtiakar et al.2006).