Chapter 1

INTRODUCTION
## Chapter 1

### INTRODUCTION

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1. Introduction

1.1. HERBAL MEDICINE & ITS USAGE

Herbal medicine is the branch of science dealing with the plant based formulations usage in the alleviating the diseases. Biodiversities in natural resources like plants, animals, microbes, marine source has served the needs for human and also useful in healthcare from immemorial times. In every era of ages there are different systems of medicine but the common thing is botanical remedies used universally. The green pharmacy from the people of preliterate societies has surprised the civilized societies with compendiums of healing herbs and this herbal healing lore was passed from generation to generation by word of mouth.

India is a varietal emporium of medicinal plants and is the richest resource of medicinal plants. The traditional system of medicine like Ayurveda, Unani and Siddha used over hundreds of plant species for combating human ailments. Ayurveda is a system of ethno medicine that takes in to consideration of the physical, psychological, philosophical and ethical well being of the human and shows great importance on living in harmony with the universe. The old definitive text “Charak Samhitha”, specifies on the complete treatment of diseases using herbs. The importance of medicinal plants and traditional systems of medicine in solving the health care problems of the world is increased nowadays. Most of the developing
countries have adopted traditional medical practice due to its advantage over the available systems.

Herbal medicines are an essential and growing part of the international pharmacopeia. The resurgence of interest in plant remedies has been spurred on by various factors like the effectiveness of plant medicine, direct source for therapeutic agents, it is easily affordable by people, these form the taxonomic markers for discovery of new compounds, these are of renewable source, the high cost; adverse effects; dissatisfaction with the results of most modern drugs and improvement in the quality safety and efficacy of herbal medicine with the development of science and technology. Antioxidants are playing a vital role in the treatment of diseases which are readily available in most of plants.\(^1\)

There is abundance in exemplifying the medicinal herbs like \textit{Rauwolfia serpentina} for hypertension, \textit{Catharanthus roseus} for leukemia, \textit{Papaver somniferum} for arthritis and insomnia \textit{Digitalis} leaves for heart therapy.\(^2\) Catechin is aflavonoid isolated from \textit{Uncaria gambir} showed to reduce the hepatotoxicity. Glycirrizhin a component licorice root (\textit{Glycyrhiza glabra}) has been used in chronic hepatitis and Silymarin a flavonoid found in milk thistle (\textit{Silybum Marianum}) has showed hepatoprotective effects.\(^3\) Quinine, theophylline, morphine, vincristine, cyclosporine are the drugs forming the corner stones of modern pharmaceutical care and they are all natural products. Herbal drugs are marketed in various forms which are
available in classical forms like capsules, lotions, syrups, ointments, creams, granules etc.

1.2. HEPATIC SYSTEM & TOXICITY

1.2.1. Structural Anatomy and Functions of Liver

The liver is the largest gland in the human body which is reddish-brown organ of unequal size and shape. It lies below the diaphragm in the abdominal-pelvic region. This organ plays a major role in metabolism and has a role in number of body physiological functions, like glycogen storage, RBC lysis, synthesis of the plasma proteins, production of the chemical mediators like hormones and detoxification. Its primary role is to control the flow and safety of substances absorbed from the digestive system before distribution of these substances into the systemic circulatory system.

The liver gets a dual blood supply from the hepatic portal vein and hepatic arteries. The spleen, gastrointestinal tract, other related organs drain the blood into the hepatic portal vein and carries venous blood. The hepatic arteries also supply blood to the liver. Oxygen is provided from both sources where a part of oxygen demand is met by the hepatic portal vein and other by the hepatic arteries.

The main Functions of liver are:

Protein metabolism

The liver deaminates (remove the amino acid, NH$_2$) from amino acids and used for the production of the energy. It converts the
resulting toxic ammonia (NH$_3$) into the much less toxic urea for excretion in urine. Hepatic cells synthesize plasma protein such as alpha and beta globulin, albumin, prothrombin and fibrinogen.

![Figure 1.1. Anatomy of liver](image)

**Carbohydrate metabolism**

The liver performs several roles in carbohydrate metabolism like Glycogenolysis, Gluconeogenesis and Glycogenesis.

**Lipid metabolism**

Liver stores some triglycerides (neutral fat) breakdown fatty acids into acetyl coenzyme-A, this process is called as oxidation and converts excess acetyl coenzyme-A into ketone bodies (Ketogenesis). Hepatic cells synthesize cholesterol and use cholesterol to make bile salts and it also synthesis lipoproteins.
Immune function

The liver consists of Kupffer cells (modified macrophage) that remove any harmful viruses, bacteria, yeast toxins and other unwanted substances from the blood.

Vitamin storage

Liver stores the vitamins like A, B12 and D and also iron.

Detoxification

Hormones, drugs, chemicals, alcohol, nicotine are deteriorated and detoxified by the liver. The liver produces and excretes bile (a yellowish liquid) required for emulsifying fats\textsuperscript{4,5}.

1.2.2. Abnormalities of Liver Functions

The abnormalities of liver functions includes hepatitis A, B, C, D, E, cirrhosis, alcohol damage, fatty liver. Elevated aminotransferases such as Alanine aminotransferases (ALT), Aspartate aminotransferases (AST), alteration in Alkaline phosphatase (ALP) and Bilirubin are found to some degree in almost all patients with liver disease and represent hepatocellular dysfunction.

The symptomatic identification of liver damage is:

- In Jaundice skin becomes yellow, eyes fade out, and mucous membranes also become white due to high levels of bilirubin in the extracellular fluid.
• Excessive fatigue occurs from generalized loss of nutrients, minerals and vitamins.

• The liver fails to synthesis albumin abdomen, ankles and feet show oedema.

• Bilirubin is mixed with urine and changes the colour of urine in to dark.

• Fever is also the characteristic symptom of liver disease.

• Occurrence of generalized itching is also seen.

• Abdominal pain and cramps occur, shows nausea and vomiting.

• Bleeding occurs continuously.

Liver injury is defined as an elevation in levels serum alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TB) by twice or thrice than normal levels. Liver injury is further characterized as hepatocellular when there is a predominant initial elevation of the alanine aminotransferase level or as cholestatic when there is a predominant initial elevation of the alkaline phosphatase level a mixed pattern comprises elevations of both the alanine aminotransferase and alkaline phosphatase levels. As drugs tend to create injury predominantly in some pattern, recognition of the pattern is necessary. The injury patterns are hepatocellular, cholestatic and sometimes mixed in pattern.
### Table 1.1. Mechanisms of hepatotoxicity by a variant of drugs

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<th><strong>Hepatocellular</strong> <em>(Elevated ALT)</em></th>
<th><strong>Mixed</strong> <em>(Elevated ALP+ALT)</em></th>
<th><strong>Cholestatic</strong> <em>(Elevated ALP+TBL)</em></th>
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### 1.2.3. Pathophysiology of the Drug-Induced Liver Injury

**Hepatocyte disruption:** Covalent binding of the drug to intracellular proteins can cause a decrease in ATP levels, leads to disruption of actin. Improper arrangements of actin fibrils at the surface of the hepatocyte cause blebs and rupture of the membrane.

**Transport proteins disruption:** Drugs that affect transport proteins at the canalicular membrane can interrupt bile flow and result in loss of villous process and interrupt of transport pumps. That develops multidrug resistance associated protein prevent the bilirubin excretion, which causes cholestasis.
Apoptosis: Activation of the apoptotic pathways by the tumour necrosis factor-alpha receptor of Fas may trigger the cascade of intercellular caspases, which results in programmed cell death.

Mitochondrial disruption: Some drugs inhibit mitochondrial function by a dual effect on both β-oxidation energy production by inhibiting the synthesis of Nicotinamide adenine dinucleotide (NADH), Flavine adenine dinucleotide (FADH), resulting in decreased ATP production.

Bile duct injury: Toxic metabolites excreted in bile may cause injury to the epithelium of the bile duct.

1.2.4. Screening methods for Hepatoprotective activity

There are two types of screening methods

In-Vitro methods

In-Vivo methods

In In-Vitro method the hepatocytes are isolated and mixed with the hepatotoxins and after 3 hrs checked for the viability of cells. Based on the viability of cells the hepatotoxicity is identified.

In In-Vivo method the animals are induced with hepatotoxins orally, and checked after 24 hrs and 48 hrs for the toxicity by biochemical estimation of ALT, AST, ALP AND BILIRUBIN levels and toxicity is identified.

Chemical reagents and drugs which induce lipolysis, necrosis, cirrhosis, carcinogenesis and hepatobiliary dysfunctions in
experimental animals are classified as hepatotoxins. The chemicals used for screening showing significant alteration in liver structure are Carbon tetrachloride (CCl₄), Thioacetamide (TAA), D-galactosamine, Paracetamol and Azathioprine (AZA).

**Carbon tetrachloride induced hepatotoxicity**

Liver injury due to Carbon tetrachloride in rats was first reported in 1936 and has been widely and successfully used by many investigators. Carbon tetrachloride is metabolized by cytochrome P-450 in endoplasmic reticulum and mitochondria with the formation of CCl₃O⁺, a reactive oxidative free radical, which initiates lipid peroxidation. Administration of a single dose of CCl₄ to a rat produces, within 24 hrs, a centrilobular necrosis and fatty changes. The poison reaches its maximum concentration in the liver within 3 hrs of administration. Thereafter, the level falls and by 24 hrs there is no CCl₄ left in the liver. The development of necrosis is associated with leakage of hepatic enzymes into serum. Dose of CCl₄ 0.1-3 ml/kg i.p.

\[
\text{CCl}_4 \rightarrow \text{CCl}_3\text{O}^+ + \text{O}^- \]

**Thioacetamide induced hepatotoxicity**

Thioacetamide interferes with the movement of RNA from the nucleus to cytoplasm which may cause membrane injury. A metabolite of thioacetamide (perhaps s-oxide) is responsible for hepatic injury. Thioacetamide reduce the number of viable hepatocytes as well as rate of oxygen consumption.
It also decreases the volume of bile and its content i.e. bile salts, cholic acid and deoxycholic acid. Dose of thioacetamide: 100 mg/kg, s.c.

**Galactosamine Induced Hepatotoxicity**

D-Galactosamine induced liver damage has been extensively used as an experimental model. Galactosamine produces diffuse type of liver injury simulating viral hepatitis. It presumably disrupts the synthesis of essential uridylic nucleotides resulting in organ injury and resulting in cell death. Depletion of those nucleotides would impede the normal synthesis of RNA and consequently would produce a decline in protein synthesis. This mechanism of toxicity brings about an increase in cell membrane permeability leading to enzyme leakage and eventually cell death. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or canalicular membrane of hepatocytes Galactosamine decrease the bile flow and its content i.e. bile salts, cholic acid and deoxycholic acid. Galactosamine reduces the number of viable hepatocytes as well as rate of oxygen consumption. Dose of D-Galactosamine: 400 mg/kg, i.p.
**Paracetamol induced hepatotoxicity**

Paracetamol is widely used analgesic and antipyretic drug. When administered in higher doses it causes undesirable side effects, such as hepatotoxicity. Paracetamol administration causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis followed by lesion in liver. The covalent binding of N-acetyl-P-benzoquinonemine, which is a product of oxidation from the Paracetamol results in lipid peroxidation and also degradation of the glutathione levels and thereby produces cellular necrosis. Dose of Paracetamol: 1g/kg p.o

**Azathioprine induced hepatotoxicity**

AZA is a drug of preferable choice in autoimmune disorders and in preventing rejection of organ grafting. AZA is cleaved in vitro in to 6-Mercaptopurine by nucleophilic attack of sulphhydryl groups primarily GSH, and results in depletion from hepatocytes and leading to mitochondrial injury with profound depletion of ATP and cell necrosis. Lipid peroxidations as well as altered levels of some endogenous scavengers are taken as indirect in vivo reliable index for the contribution of free radical generation and resulting in oxidative stress.

**1.2.5. Medicinal plants for Hepatoprotective activity**

Modern drugs have least possibility of alleviation in hepatic ailments, available commercial allopathic drugs to treat liver disorders also cause further detrimental effects to the liver and herbal drugs has
grown popularity in treating the conditions. The limiting factors contribute for less usage of herbal drugs i) Lack of standardization procedure for herbs; ii) Identification of active ingredient is complex with many components in crude iii) Randomized clinical trials are not done.

The phytoconstituents used for liver diseases chiefly on regional basis include drugs like Silymarine (Silybum marianum) and Catechin (Anacardium occidentalis) in Europe, Glycyrrhizin (Glycyrrhiza glabra) in Japan and chizandrins (Schizandra chinesis) in China are of at most important in treatment of the hepatic diseases. Extract of about 25 different plants have been reported liver diseases.

*Tinospora cardifolia Willd* is a well known Hepatoprotective herb mentioned and used in Ayurveda. The other medicinal plants of Hepatoprotective activity include, Phenols as main constituent in Arnica Montana Linn, Cichorium intybus, Linn. Picrorriza kurroa Royle, Syzygium aromaticum Linn, Flavonoids as main constituent in Acacia catechu Willd, Aegiceras corniculatum, Artemisia capillaries Thunb, Calotropis gigantean R.Br, Tagetes patula Linn, Uncaria gambir (Hunter) Roxb, Alkaloids as main constituent in Aristolochia clematis, Fumaria parviflora Lam, Fumaria officinalis Linn, Herniaria glabra Linn, Peumus boldus Molina, Physalis peruviana, Boerhaavia diffusa, Alhagi maurorum, Saussurea amara Salsola collina Pall., Achillea asiatica Serg and rhizomes of Glycyrrhiza uralensis Fisch.
1.3. IMMUNITY AND IMMUNOMODULATION

1.3.1. Immunity & its Types

Immunity is the ability of the body to defend itself against specific invading agents such as bacteria, toxins, viruses and foreign tissue is called specific resistance (or) immunity. Immunity is classified

I. Innate (Native) Immunity (a) Nonspecific (b) Specific

II. Acquired (Adaptive) Immunity

(a) Active 1. Natural
2. Artificial

(b) Passive 1. Natural
2. Artificial

III. Immunomodulation

_Innate immunity_

Innate immunity may be considered at the level of the species, race or individual. Species immunity refers to the total or relative refractoriness to a pathogen, shown by all members of species. Within a species, different races may show differences in susceptibility to infection. This is known as racial immunity. Such racial differences are known to be genetic in origin, and by selection and inbreeding, it is possible to develop that possess high degrees of resistance or susceptibility to various pathogens.
The difference in innate immunity exhibited by different individuals in a race is known as individual immunity. The genetic basis of individual immunity is evident from studies on the incidence of infectious diseases in twins. It is well documented that homozygous twins exhibit similar degrees of resistance or susceptibility to lepromatous leprosy and tuberculosis. Such correlation is not seen in heterozygous twins\textsuperscript{14}.

**Mechanisms of innate immunity**

The **Epithelial surfaces** of intact skin and mucous membrane covering the body protect it considerably against invasion by microorganisms. They provide much more than a mechanical barrier. Healthy skin possesses bactericidal activity to which the presence of high concentration of salt in drying sweat, sebaceous secretions and long chain fatty acids and soaps contribute. The bactericidal activity of skin secretions is illustrated by the frequent mitotic and phylogenetic infections seen in persons who immerse their hands in soapy water for long periods occupationally.

The mucosa of the **respiratory tract** has several innate mechanisms of defense. The very architecture of the nose prevents entry of microorganisms to a large extent the beyond are held by the mucus lining the epithelium, and are swept back to the pharynx where they tend to be swallowed or coughed out. The cough reflex is an important defense mechanism of the respiratory tract. The cilia on
the respiratory epithelial cells propel particles upwards. Nasal and respiratory secretions contain mucopolysaccharides capable of combining with influenza and certain other viruses. Particles that manage to reach the pulmonary alveoli are ingested by the phagocytic cells present there.

The **mouth** is constantly bathed in saliva which has an inhibitory effect on many microorganisms. Particles deposited in the mouth are swallowed and subjected to the action of the digestive juices. The high acidity of the stomach destroys most microorganisms. The pH becomes progressively alkaline from the duodenum to the ileum. The ileum contains rich and varied flora and in the large intestine, the bulk of the content is composed of bacteria.

The **conjunctiva** is freed of foreign particles by the flushing action of lachrymal secretions. The eyes become susceptible to infection when lachrymal secretions are absent tears contain the antibacterial substances lysozyme and this is thermo labile, low molecular weight basic protein called as a muraminidase. Lysozyme is present in the tissue fluids and in nearly all secretions except cerebrospinal fluid, sweat and urine. It acts by splitting certain polysaccharide components of the cell walls of susceptible bacteria, in the concentrations seen in tears and other secretions lysozyme is active bacteria.
Several substances possessing antibacterial properties have been described in blood and tissues. Beta lysine is a relatively thermostable substance which is active against anthrax and related bacilli. Basic polypeptides such as leukins extracted from leukocyte and plakins from platelets also are acting as antibacterial substances. Acidic substances, such as lactic acid found in muscle tissue and in the inflammatory zones, Lactoperoxidase in milk also possess antibacterial properties.

**Cellular factors in innate immunity**

Phagocytic cells were originally classified in to microphages and macrophages. Microphages are polymorphonuclear leukocytes. Macrophages consist of histocytes which are the wandering amoeboid cells seen in tissues, the fixed reticuloendothelial cells and the monocytes in the blood. A major function of the reticuloendothelial system is the removal of foreign particles that enters the body. Phagocytic cells reach the sites of inflammation in large numbers, attracted by chemotactic substances, and ingest particulate material. Classes of lymphocytes called natural killer cells are important in nonspecific defense against viral infections and tumours. They selectively kill virus infected cells and tumour cells. NK cells are activated by Interferons\textsuperscript{14}. 
**Inflammation**

Tissue injury or irritation, initiated by the entry of pathogens or other irritants, leads to inflammation, is an important non-specific defense mechanism. The arterioles at the site constrict initially and then dilate leading to increased blood flow and imagination of the leukocytes which escape into the tissues by diapedesis and accumulate in large numbers attracted by the chemotactic substances released at the site of injury. Microorganisms are phagocytosed and destroyed. There is an outpouring of plasma, helping to dilute the toxic products present. A fibrin barrier is laid serving to wall of the site of infection.

**Acquired Immunity**

The resistance that an individual acquires during life is known as acquired immunity, as distinct from inborn innate immunity. Acquired immunity is of two types active and passive.

Active immunity is the resistance developed by an individual as a result of an individual as a result of antigenic stimulus. It is also known as adaptive immunity as it represents the adaptive response of the host to a specific pathogen or other antigen.

This involves the active functioning of the host’s immune apparatus leading to the synthesis of antibodies and the production of immunologically active cells. Active immunity sets in only after a latent period which is required for the immunological machinery to be
set in motion. During the development of active immunity, there is often a negative phase during which the level of measurable immunity may actually be lower than it was before the antigenic stimulus. This is because the antigen combines with any pre-existing antibody and lowers its level in circulation.

Once developed, active immunity is long-lasting if an individual who has been actively immunized against an antigen experiences the same antigen subsequently, the immune response occurs more quickly and abundantly than during the first encounter. This is known as secondary response. The development of humoral and cellular immunity is associated with immunological memory. This implies that the immune system is able to retain for long periods the memory of a prior antigenic exposure and to produce secondary type of response when it encounters the same antigen again.

Active immunization is more effective and confers better protection than passive immunization. Active immunity may be natural or artificial. Natural active immunity results from either a clinical or an in apparent infection by a microbe. A person who has recovered from an attack of measles develops natural active immunity.

*Artificial Active Immunity* is the resistance induced by vaccines. Vaccines are preparations of live or killed microorganisms or their products used for immunization.
1. Bacterial vaccines
   a. Attenuated (BCG vaccine for tuberculosis)
   b. Killed (Cholera vaccine)
   c. Subunit (Typhoid Vi antigen)
   d. Bacterial products (Tetanus Toxoid)

2. Viral vaccines
   a. Attenuated (Oral polio vaccine-Sabin)
   b. Killed (Injectable polio vaccine-Salk)
   c. Sub unit (Hepatitis B vaccine)

**Passive immunity**

The resistance that is transmitted passively to a recipient in a 'readymade' form is known as passive immunity. Here the recipient’s immune system plays no active role.

There is no antigenic stimulus instead, performed antibodies are administered. There is no latent period in passive immunity, protection is being effective immediately after passive immunization. There is no negative phase. The immunity is transient, usually lasting for days or weeks, only till the passively transmitted antibodies are metabolized and eliminated. No secondary type response occurs in passive immunity. In fact, passive immunity diminishes in effect with repetition. When a foreign antibody is administered a second time, it is eliminated more rapidly than initially. Following the first injection of
an antibody such as immune horse serum, the elimination is only by metabolic break down but during subsequent injections of horse serum, elimination is much quicker as it combines with antibodies to horse serum that would have been produced following its initial injection. This factor of immune elimination limits the usefulness of repeated passive immunization.

Passive immunization is less effective and provides an immunity inferior to that provided by active immunization. The main advantage of passive immunization is that it acts immediately and, therefore, can be employed when ‘instant’ immunity is desired.

*Natural passive immunity* is resistance passively transferred from mother to baby. In human infants, maternal antibodies are transmitted predominantly through the placenta, the human colostrums, which is also rich in IgA antibodies resistant to intestinal digestion, gives protection to the neonate. Transport of antibodies across the placenta is an active process and therefore the concentration of antibody in fetal blood may sometimes be higher than that seen in the mother.

*Artificial passive immunity* is the resistance passively transferred to a recipient by the administration of antibodies. The agents used for this purpose are hyper immune sera of animal or human origin, convalescent sera and pooled human gamma globulin. These are used for prophylaxis and therapy.
Sometimes a combination of active and passive methods of immunization is employed. This is known as *combined immunization*. A special type of immunization is the injection of immunologically competent lymphocytes. This is known as *adaptive immunity* and does not have general application. Instead of whole lymphocyte, an extract of immunologically competent lymphocytes, known as the “transfer factor”, can be used. This has been attempted in the treatment certain types of diseases (Lepromatous leprosy)\textsuperscript{14}.

1.3.2. Immunomodulation and Drugs

Modification of the immune response or the functioning of the immune system by the action of a drug or any chemical ligand is said to be immunomodulation. Immunotherapy is a medical term defined as the "treatment of disease by inducing, enhancing, or suppressing an immune response." Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies, while immunotherapies that reduce or suppress are classified as suppression immunotherapies. Immunomodulation has an effect on the immune system in different ways with variety of substances, behavioural changes, dietary modification, etc. Immune system dysfunction is responsible for various disease like arthritis, ulcerative colitis, asthma, allergy, parasitic disease, cancer and infectious disease\textsuperscript{14}. 
Immunomodulators are substances that alters the immune response by augmenting or reducing the ability of the immune system to produce antibodies or sensitized cells that recognize and react with the antigen that initiated their production. Immunomodulators include corticosteroids, cytotoxic agents, thymosin, and immunoglobulins. Some immunomodulators are naturally present in the body, and certain of these are available in pharmacologic preparations\textsuperscript{15}.

**Immunosuppressant drugs**

These have major role in organ transplantation and auto immune diseases.

- **Calcineurin inhibitors:** Cyclosporine, Tacrolimus.
- **Antiproliferative drugs:** Azathioprine, Cyclophosphamide, Methotrexate, Chlorambucil, Mycophenolate mofetil (MMF)
- **Glucocorticoids:** Prednisolone
- **Antibodies:** Muromonab CD3, Anti-Thymocyte Globin(ATG), Rho(D), Efalizumab.

**Immunostimulants**

These have the role in treatment of infectious diseases in improving the body immune response on to the xenobiotic agents.
**Levamisole:** It is an antihelminthic drug that also restores functions of B lymphocytes, T lymphocytes, monocytes and macrophages. Hence it has been used in colon cancer along with 5-fluorouracil.

**Thalidomide:** Anti-angiogenesis, Rheumatoid arthritis: Anti TNF effect.

**Recombinant cytokines:** Interferon used in tumors and chronic hepatitis B and C. Interleukin 2 (aldeslukin) has been used in renal cell carcinoma and melanoma\textsuperscript{15}.

### 1.3.3. Medicinal plants for Immunomodulation

The screening of compounds has revealed many compounds with phytoconstituents like Alkaloids, Flavonoids, and Terpenoids possessing anti-inflammatory activity, anticancer and immunostimulation. *Abutilon indicum\textsuperscript{16}, Tinospora cardifolia\textsuperscript{17}, Viscum Album, Panax ginseng, Asparagus racemosus, Polygala senega\textsuperscript{18} and Ocimum Sanctum\textsuperscript{19} Achillea wilhelmsii\textsuperscript{20} Stachytarpheta cayennensis\textsuperscript{21} Ocimum basilicum\textsuperscript{22} Grewia asiatica\textsuperscript{23} are the plants with established activity of immunomodulatory.

### 1.3.4. Screening of Immunomodulation

Measurement of immunity is done by demonstration of antibodies by a variety of techniques such as agglutination, precipitation, complement fixation, haemagglutination inhibition, neutralization, neutrophils adhesion, carbon clearance by phagocytosis, delayed type hypersensitivity and ELISA\textsuperscript{24}. 