2. REVIEW LITERATURE

2.1. Cancer

Cancer is a disease of misguided cells which have high potential of excess proliferation without apparent relation to the physiological demand of the process. Cancer is the second leading causes of death in the United States, with one of every four deaths attributable to cancer (Jemal et al., 2006). There are more than 100 types of cancer. More than 50% of this occur in five major organ i.e. lungs, colon, rectum, Breast, Prostate and uterus. Cancer of lung, colon and prostate are the principle leading causes of death in males, whereas breast and uterus cancer are most common in females. Cancer cell are usually degenerate and are capable of only reproducing themselves. In many parts of the world there is a dramatic shift in cancer occurrence. In several newly industrialized region cancer is becoming one of the leading cause of death (Durairaj et al., 2009; Goyal, 2007).

Cancers are classified according to the tissue and cell type from which they arise. Cancers that develop from epithelial cells are called carcinomas; those arising from connective tissue or muscles are called sarcomas; and those arising from blood-forming tissue, such as the bone marrow, are known as leukemia. More than 90 percent of all human cancers are carcinomas (Joseph et al., 2005).

2.1.1 Types of tumor

The terms cancer, malignant neoplasm and malignant tumor are synonymous; they are distinguished from benign tumor by the properties of dedifferentiation, invasiveness and the ability to metastasis (Spread to other parts of the body). Neoplasm or Tumor is defines as “An abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and which persists in the same excessive manner after cessation of the stimulus which has evolved the change” Neoplasia literally means new growth. Neoplasm may be of two types: (a) Benign Neoplasm (b) Malignant Neoplasm.
(a) Benign Neoplasm
A neoplasm grows without invading adjacent tissue or spreading to distant sites. It is usually fairly well-circumscribed due to the lack of invasion of surrounding tissues.
Benign Neoplasm is characterized by:
- Well-differentiated cells that resemble their normal for bearers.
- Slow and progressive growth that may come to a standstill or regress.
- Growth by expansion with the formation of a capsule.
- Absence of metastasis.

(b) Malignant Neoplasm
A malignant neoplasm invades and destroys the surrounding tissue. In fact the name cancer arose from the first descriptions of malignancies in which claw-like projections were noted to be extending from the central tumor. These claws resembled those of a crab or cancer. A neoplasm that invades the surrounding normal tissue usually spreads to distant sites given sufficient time.
Malignant neoplasm are characterized by
- Anaplasia or poorly differentiated cells.
- Rapid and often erratic growth with many abnormal mitotic figures.
- Growth by infiltration as well as by expansion and a well-defined capsule is almost always absent frequent metastasis.

2.1.2 Causes of Cancer (Neoplasia)
There have been numerous theories advanced to explain the cause of neoplasms. However, the factor or factors responsible for the development of most neoplasms still remains unknown. The numerous agents capable of producing neoplasia naturally and experimentally can be grouped as follows (Danaei et al., 2005; Buell et al., 1965)
   a) Carcinogenic chemicals.
   b) Oncogenic viruses.
   c) Environmental factor and other agents.
   d) Diet
e) Heredity

a) Carcinogenic chemicals:
Most chemical carcinogens act by producing changes in DNA. Occasionally they cause changes in growth regulating proteins without producing genetic abnormality. There are 2 types of carcinogens.

- **Direct-acting carcinogens**: These carcinogens act locally at the site of application without having to undergo metabolic changes in the body.
- **Ultimate carcinogens**: These are carcinogens that are converted into metabolically active compounds within the body. These compounds are called procarcinogens. Examples of chemical carcinogens are Polycyclic hydrocarbons, Cigarette smoking, Aromatic amines, Cyclamates and saccharin, Azo dyes, Nitros amines, Anti-cancer drugs.

b) Oncogenic viruses:
A number of viruses can infect mammalian cells and transforming them into cancer cells those viruses known as oncogenic viruses. It contains either DNA or RNA as their genome. These viruses are broadly divided in two groups.

- **Oncogenic RNA viruses (Retro-viruses)** cause many neoplasms in experimental animals. Examples include leukemia, lymphoma in mice, sarcoma in birds and primates and breast cancer in mice (Bittner milk factor or mouse mammary tumor viruses).
- **Oncogenic DNA viruses**: Several groups of DNA viruses have been implicated as the cause of human neoplasms. Examples include Papilloma viruses, Epestein-Barr Virus (EBV), Herpes Simplex Virus (HSV) type 2, Cytomegalovirus (CMV).

c) Environmental factor and other agents:
The majority of cancer risk factors are environmental or lifestyle-related in nature, leading to the claim that cancer is a largely preventable disease. Examples of modifiable cancer risk factors include alcohol consumption (associated with increased risk of oral, esophageal, breast, and other cancers), smoking (although 20% of women with lung cancer have never smoked, versus 10% of men), physical inactivity (associated with increased risk of colon, breast, and possibly
other cancers), and being overweight / obese (associated with colon, breast, endometrial and possibly other cancers).

d) Diet:
Diet is also a source of number of chemicals that can initiate Cancer. Poly nuclear aromatic hydrocarbons, N- nitroso compounds, heterocyclic amines and aromatic amines are some well-known examples of environmental chemicals that can act as initiators of carcinogenesis. These chemicals are known to be common dietary contaminants potent carcinogens, derived from molds such as mycotoxins and aflatoxins may also contaminate foods. All the aforementioned carcinogens as well as age, sex, environment, tobacco use, growth factors and chronic irritation are among the factors considered to be promoters of carcinogenesis.

e) Heredity:
Most forms of cancer are sporadic, meaning that there is no inherited cause of the cancer. There are, however, a number of recognized syndromes where there is an inherited predisposition to cancer, often due to a defect in a gene that protects against tumor formation.

2.1.3 Genesis of cancer
The development of cancer is a complex multistage process involving not only a genetic change but also other factor that are not in themselves cancer producing however they increases the genesis of cancer. There are two main categories of genetic change that lead to cancer (Robbins et al., 2007; Karp et al., 2008).
1. Activation of proto-oncogenes to oncogenes.
2. Inactivation of tumor suppressor gene.
Oncogenes are those genes that confer malignancy on a cell. Proto-oncogene is genes that normally promote cell division and differentiation and they may get converted into oncogenes. Similarly there are some genes that keep a check on cell- division. They are known as tumor suppressor genes (Gandhi, 2000).
Cell Cycle of Neoplastic Cell

Both the cancer and normal cell reproduces in a series of steps known as cell cycle. The cell cycle consists of four stages or phases: cell division (M phase, for mitosis); a gap immediately after M phase, called G₁; DNA synthesis (S phase); followed by another gap, called G₂. The cycle includes three checkpoints: the first is a DNA damage checkpoint that occurs in G₁. The monitors check for damage that may have occurred as a result of the last cell cycle or were caused by something in the environment, such as UV radiation or toxic chemicals. If damage is detected, DNA synthesis is blocked until it can be repaired. The second checkpoint occurs in G₂, where the monitors make sure errors were not introduced when the chromosomes were duplicated during the S phase. The G₁ and G₂ checkpoints are sometimes referred to collectively as DNA damage checkpoints. The third and final checkpoint occurs in M phase, to ensure that all of the chromosomes are properly attached to the spindle. This checkpoint is intended to prevent gross abnormalities in the daughter cells with regard to chromosome number. If a chromosome fails to attach to the spindle, one daughter cell will end up with too many chromosomes, while the other will have too few. The T cells of our immune system can detect abnormal, potentially dangerous cells, and when they do they order those cells to commit suicide. The gross changes in a cancer cell’s genetic structure, however, often knock out its ability to respond to those signals. When this happens, the cancer cell has gained immunity to apoptosis and is well on its way to fulfilling its quest for immortality and assuming the lifestyle enjoyed by its protozoan ancestors.
Many more morphological, biological and biochemical changes are seen in cancer cells such as following (Dipiro et al., 1993).

Morphological changes

- Cancer cells are usually rounded shape larger than the normal cell. Cancer cells show nuclear and cellular pleomorphism, hyper chromatist and altered nuclear.
- Cancer cell often grow over one another and from multilayer.
- Cancer cell have least adhesion capacity and grow without attachment to the surface in vitro.
- Large nucleoli are present.
- Nuclear chromatin is often coarsely clumped and distributed along the nuclear membrane.

Biochemical Changes

- Increase the turnover of the nucleic acid, DNA and RNA.
- Enhanced glycolysis in both aerobic and anaerobic.
• Alteration in cell permeability and cell surface change.
• Increased activity of ribonucleotide reductase.
• Secrete certain protein kinase.
• Cancer cells show appearance of new antigen and loss of certain normal antigen.
• Exhibit inappropriate synthesis of certain hormones and growth factor.

2.1.4 Prevention and cure of cancer
Prevention, by drugs, of the change that converts a normal cell to an invasive malignant cell has only now begun to be attained (Hogland et al., 1982; Laurence et al., 1997). Some cancers can be prevented, wholly or in part, by protecting people or inviting them to protect themselves from exposure to known carcinogens (industrial cancers, bronchial cancer). Usual mode of treatment to achieve cure or remission can be achieved by following means.
(a) Surgery for solid tumors
(b) Radiation therapy
(c) Chemotherapy – Use of drugs like cytotoxic drugs, hormones
(d) Immunotherapy
(e) Hormone therapy

a) Surgery
Surgery offers the greatest chance for cure for many types of cancer, especially those that have not spread to other parts of the body. In some cases, a margin of healthy tissue and nearby lymph nodes may also be removed to try to prevent spread of the cancer. Surgery may be used to treat cancer when it is first diagnosed. When the cancer cannot be cured, surgery is sometimes used to help control the disease and alleviate symptoms.

The more common types of cancer surgeries are listed here.
• Preventive (prophylactic) surgery
• Diagnostic surgery
• Staging surgery
• Curative surgery
Debulking (cytoreductive) surgery
Palliative surgery
Supportive surgery

b) Radiation therapy (Radiotherapy)
Radiation therapy, or radiotherapy, directs high-energy rays at a cancer site to stop cells from growing and dividing. It may be used before surgery to shrink the tumor or after surgery to destroy any remaining cancer cells. In external radiation therapy, a machine beams the rays at the cancer. In some cases, an implant containing a radioactive substance may be inserted into the tumor to deliver a higher dose of radiation than is possible externally.

Types of Radiation Used to Treat Cancer:
Radiation used for cancer treatment is called ionizing radiation because it forms ions in the cells of the tissues it passes through as it dislodges electrons from atoms. This can kill cells or change genes so the cells cannot grow. Other forms of radiation such as radio waves, microwaves and light waves are called non-ionizing. They don't have as much energy and are not able to ionize cells.
Ionizing radiation can be sorted into two major types
- Photons: x-rays and gamma rays, which are most widely used.
- Particle radiation: electrons, protons, neutrons, alpha particles, and beta particles.
Some types of ionizing radiation have more energy than others. The higher the energy, the more deeply the radiation can penetrate the tissues. The more common sources of radiation used for cancer treatment are High-energy photons that come from radioactive sources such as cobalt, cesium, or a machine called a linear accelerator.

c) Chemotherapy
Chemotherapy uses anticancer drugs, singly or in combination, to treat cancer. The drugs may be given by mouth or injected into a vein or muscle. Because anticancer drugs can reach cancer cells in nearly every part of the body, chemotherapy may be used as a primary treatment for cancers that have spread.
One of the major difficulties in the use of cancer chemotherapy is that a tumor is usually far advanced before it is diagnosed (Sharma, 2004; Lecouter et al., 2001). Anti Cancer drugs are also classified into two categories according to cell kinetic and dose strategy.

**Cell-Cycle Phase- Dependent Drugs:**
These drugs act chiefly on cells in certain phases of the cell cycle e.g. Drugs like methotrexate, mercaptopurine, Flurouracil acting on S phase and vinca alkaloids on M Phase.

**Cell-Cycle Phase- Independent Drugs:**
Cell-Cycle Phase-Independent drugs act on cells in any phase of the cycle including a slight effect on the G₀ Phase. Cyclophosphamide, doxorubicin and cisplatin are phase independent drugs. They are equally effective in tumors where the growth fraction.

The main anticancer drugs can be divided into the following general categories.

**Cytotoxic drugs**
- Alkylating agents and related compounds which act by forming covalent bonds with DNA and thus impeding replication.
- Antimetabolites, which block or subvert one or more of the metabolic pathways involved in DNA synthesis.
- Cytotoxic antibiotics, i.e. substances of microbial origin that prevent mammalian cell division.
- Plant derivatives (Vinca alkaloids, Taxanes, Campothecins) most of these specifically affect microtubule function and hence the formation of the mitotic spindle.
- Hormones of which the most important are steroids, namely glucocorticoids, oestrogens and androgens, as well as drugs that suppress hormone secretion or antagonise hormone action.
- Miscellaneous agents that do not fit into the above categories. This group includes a number of recently developed drugs designed to affect specific tumor-related targets.
d) Immunotherapy

Biological therapy, or immunotherapy, uses substances that stimulate the body's immune system to fight the cancer or reduce side effects from treatment. These substances include monoclonal antibodies, interferons, interleukins, tumor necrosis factor and cancer vaccines (Crommelin et al., 2007).

Role of plants in cancer chemotherapy

Plant materials have been used in the treatment of malignant disease for centuries. A comprehensive survey of the literature, both old and new, on plants used against cancer shows a list of over 1400 genera. Vinblastine (VLB) and vincristine (VCR) from catharahtus roseus, epipodophyllotoxin (an isomer of podophyllotoxin) from podophyllum species, Paclitaxel (taxol) from the bark of Taxus brevifolia were highly used as anticancer agents from plant resources (Cragg at al., 2005).
2.2 Arthritis

The term *arthritis* is derived from the Greek: “arthron” meaning “joint” and “itis” meaning inflammation. This is pain and/or inflammation of the joints and may be associated with stiffness, swelling and deformity. The most common form, osteoarthritis (degenerative joint disease) is a result of trauma to the joint, infection of the joint, or age. Other arthritis forms are rheumatoid arthritis, psoriatic arthritis, and related autoimmune diseases. Septic arthritis is caused by joint infection. Pain is often a constant and may be localized to the joint affected. The pain from arthritis occurs due to inflammation that occurs around the joint, damage to the joint from disease, daily wear and tear of joint, muscle strains caused by forceful movements against stiff, painful joints and fatigue (Satoskar, 2001).

Rheumatoid arthritis is traditionally considered a chronic, inflammatory autoimmune disorder that causes the immune system to attack the joints. It is a disabling and painful inflammatory condition, which can lead to substantial loss of mobility due to pain and joint destruction.

RA is a systemic disease, often affecting extra-articular tissues throughout the body including the skin, blood vessels, heart, lungs, and muscles. Autoimmune diseases are illnesses that occur when the body tissues are mistakenly attacked by own immune system. Patients with autoimmune diseases have antibodies in their blood that target their own body tissues, where they can be associated with inflammation. Because it can affect multiple other organs of the body, rheumatoid arthritis is referred to as a systemic illness and is sometimes called rheumatoid disease.
A joint is where two bones meet to allow movement of body parts. Arthritis means joint inflammation. The joint inflammation of rheumatoid arthritis causes swelling, pain, stiffness, and redness in the joints. The inflammation of rheumatoid disease can also occur in tissues around the joints, such as the tendons, ligaments, and muscles. In some patients with rheumatoid arthritis, chronic inflammation leads to the destruction of the cartilage, bone and ligaments causing deformity of the joints. Damage to the joints can occur early in the disease and be progressive. The progressive damage to the joints does not necessarily correlate with the degree of pain, stiffness, or swelling present in the joints (Fig. 2.2).

2.2.1 Types of Arthritis

a) Rheumatoid arthritis:-

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints. Rheumatoid arthritis can also cause inflammation of the tissue around the joints, as well as in other organs in the body. Autoimmune diseases are illnesses that occur when the body's tissues are mistakenly attacked by their own immune system. The immune system contains a complex organization of cells and antibodies designed normally to "seek and destroy" invaders of the body, particularly infections. Patients with autoimmune diseases have antibodies in their blood that target their own body tissues, where they can be associated with inflammation. Because it can affect multiple other organs of the body, rheumatoid arthritis is referred to as a systemic illness and is sometimes called
rheumatoid disease. However, rheumatoid arthritis is typically a progressive illness that has the potential to cause joint destruction and functional disability.

b) Osteoarthritis:-
Osteoarthritis is the most common form of arthritis. It can affect both the larger and the smaller joints of the body, including the hands, feet, back, hip or knee. The disease is essentially one acquired from daily wear and tear of the joint. Osteoarthritis begins in the cartilage and eventually leads to the two opposing bones eroding into each other. Initially, the condition starts with minor pain while walking but soon the pain can be continuous and even occur at night. The pain can be debilitating and prevent one from doing any type of activity. Osteoarthritis typically affects the weight bearing joints like the back, spine and pelvis. Unlike rheumatoid arthritis, osteoarthritis is a disease of the elderly. Risk factors for osteoarthritis include: prior joint trauma, obesity, sedentary lifestyle (Vanitallie et al., 2010).

c) Psoriatic arthritis:
Psoriatic arthritis is a potentially serious inflammatory form of arthritis that is often found in association with psoriasis. With psoriasis, most individuals develop the skin problem first and then the arthritis. The typical features are of continuous joint pains, stiffness and swelling. The disease does recur with periods of remission but there is no cure for the disorder. A small percentage develops a severe painful and destructive form of arthritis which destroys the small joints in the hands and can lead to permanent disability and loss of hand function (Kleinert et al., 2007).

d) Polymyalgia rheumatic:
This is an inflammatory condition affecting muscles in and around the shoulder, upper arms, buttocks and thighs. The cause is not known. It starts suddenly and there is stiffness and restricted movement. Joints are not affected. Tiredness, weight loss and appetite loss are also symptoms. The disease can be treated with steroids.
e) Ankylosing spondylitis:
It is an inflammatory form of arthritis. It affects the joints in the lower back. They become inflamed and stiff. It usually occurs in the spine but may occur in the shoulders and sometimes the hips, only occasionally in the knees and ankles. Fatigue is common. Painful and blood shot eyes may occur (iritis). This needs immediate treatment to avoid damage to the eye. Severe disease can be disabling. Exercise is the best form of treatment.

f) Reactive arthritis:
Reactive arthritis is joint inflammation that is a “reaction” to an infection in the body. “Inflammation” is the way tissues react to injury or disease. It can cause swelling, redness, heat, and pain. Besides inflamed joints, reactive arthritis can have two other symptoms: red and inflamed eyes and an inflamed urinary tract. These symptoms may occur alone, together, or not at all. Reactive arthritis is also known as Reiter’s syndrome. Sometimes, reactive arthritis is set off by an infection in the bladder, which holds urine, or the urethra, which carries urine out of the body. In women, an infection in the vagina can spark the reaction.

g) Gout:
Gout is caused by deposition of uric acid crystals in the joint, causing inflammation. There is also an uncommon form of gouty arthritis caused by the formation of rhomboid crystals of calcium pyrophosphate known as pseudo gout. In the early stages, the gouty arthritis usually occurs in one joint, but with time, it can occur in many joints and be quite crippling. The joints in gout can often become swollen and lose function.

Symptoms of rheumatoid arthritis
Although rheumatoid arthritis can have many different symptoms, joints are always affected. Rheumatoid arthritis almost always affects the joints of the hands (such as the knuckle joints), wrists, elbows, knees, ankles, and/or feet. The larger joints, such as the shoulders, hips, and jaw may be affected. The vertebrae of the neck are sometimes involved in people who have had the disease for many years. Usually at least 2 or 3 different joints are involved on both sides of the
body, often in a symmetrical (mirror image) pattern. The usual joint symptoms include the following:

- **Stiffness**: The joint does not move as well as it once did. Its range of motion (the extent to which the appendage of the joint, such as the arm, leg, or finger, can move in different directions) may be reduced. Typically, stiffness is most noticeable in the morning and improves later in the day.
- **Inflammation**: Redness, tenderness, and warmth are the hallmarks of inflammation.
- **Swelling**: The area around the affected joint is swollen and puffy.
- **Nodules**: These are hard bumps that appear on or near the joint. They often are found near the elbows. They are most noticeable on the part of the joint that juts out when the joint is flexed.
- **Pain**: Pain in rheumatoid arthritis has several sources. Pain can come from inflammation or swelling of the joint and surrounding tissues or from working the joint too hard. The intensity of the pain varies by the individual.

**Other Symptoms**

- Malaise (blah feeling)
- Fever
- Fatigue
- Loss of appetite
- Weight loss
- Myalgias (muscle aches)
- Weakness or loss of energy

The symptoms usually come on very gradually, although in a small number of people they come on very suddenly.

### 2.2.2 Causes of rheumatoid arthritis

The cause of rheumatoid arthritis is unknown. Even though infectious agents such as viruses, bacteria, and fungi have long been suspected, none has been proven as the cause. The cause of rheumatoid arthritis is a very active area of worldwide research. Some scientists believe that the tendency to develop
Chapter 2

Review literature

Rheumatoid arthritis may be genetically inherited. It is suspected that certain infections or factors in the environment might trigger the immune system to attack the body’s own tissues, resulting in inflammation in various organs of the body such as the lungs or eyes. Regardless of the exact trigger, the result is an immune system that is geared up to promote inflammation in the joints and occasionally other tissues of the body. Immune cells, called lymphocytes, are activated and chemical messengers (cytokines, such as tumor necrosis factor/TNF and interleukin-1/ IL-1) are expressed in the inflamed areas (Tripathi, 2006).

Environmental factors also seem to play some role in causing rheumatoid arthritis. Recently, scientists have reported that smoking tobacco increases the risk of developing rheumatoid arthritis. Rheumatoid arthritis should not be confused with other forms of arthritis, such as osteoarthritis or arthritis associated with infections. Rheumatoid arthritis is an autoimmune disease. This means that the body’s immune system mistakenly attacks the tissues it is supposed to protect.

The immune system produces specialized cells and chemicals, which are released into the bloodstream and begin to attack body tissues. This response causes abnormal growth and inflammation in the synovium, the membrane that lines the joint. This process is called synovitis and is the hallmark of an inflammatory arthritis such as rheumatoid arthritis. As the synovitis expands inside and outside of the joint, it can damage the bone and cartilage of the joint and the surrounding tissues, such as ligaments, tendons, nerves, and blood vessels. Rheumatoid arthritis most often affects the smaller joints, such as those of the hands and/or feet, wrists, elbows, knees, and/or ankles. The symptoms often lead to significant discomfort and disability. Although rheumatoid arthritis most often affects the joints, it is a disease of the entire body.

It can affect many organs and body systems besides the joints such as musculoskeletal structures, skin, heart, lungs, digestive tracts, kidneys, Blood vessels, blood and eyes. Rheumatoid arthritis affects all ages, races, and social and ethnic groups. It is most likely to strike people aged 35-50 years, but it can
occur in children, teenagers, and elderly people (a similar disease affecting young people is known as juvenile rheumatoid arthritis).

2.2.3 Pathophysiology

(a) Joint Damage in Rheumatoid Arthritis

An inflamed synovium is central to the pathophysiology of rheumatoid arthritis. The synovium is infiltrated by lymphocytes, macrophages and polymorphonuclear cells (PMNs) as well as increased expression of cytokines such as TNF α , IL-1 etc. As the disease becomes established, cartilage and bone erosion occur associated with a proliferative synovitis and the release of proteolytic enzymes. An excess of synovial fluid production is a feature of active RA and there is an imbalance between the production of pro and anti-inflammatory cytokines with the balance being shifted in favor of the proinflammatory cytokines such as IL-1, IL-6 and TNF α.

In the normal knee joint, the synovium consists of a synovial membrane (usually one or two cells thick) and underlying loose connective tissue. Synovial-lining cells are designated type A (macrophage-like synoviocytes) or type B (fibroblast-like synoviocytes) (Goodman and Gilman, 2011).

![Disequilibrium of Cytokines in Joints of Patients with Rheumatoid Arthritis](image)

**Figure: 2.3 Disequilibrium of cytokines in joints of patients with rheumatoid arthritis.**

In the first weeks of the disease, tissue edema and fibrin deposition are prominent and can manifest clinically as joint swelling and pain. Within a short period, the synovial lining becomes hyperplastic and hypertrophic. An extensive network of new blood vessels is formed in the synovium (Fig. 2.3). T cells and B
cells (some of which become plasma cells) infiltrate the synovial membrane. These cells are also found in the synovial fluid, along with large numbers of neutrophils. In the early stages of rheumatoid arthritis, the synovial membrane begins to invade the cartilage. In established RA, the synovial membrane becomes transformed into inflammatory tissue, the *pannus*. The formation of locally invasive synovial tissue - pannus is a characteristic feature of rheumatoid arthritis this tissue is involved in the joint erosions seen in rheumatoid arthritis.

**Figure 2.4: Major anatomical features of inflamed joint in rheumatoid arthritis**

This fig. 2.4 shown the synovium highlights type A (macrophage -like) and type B (fibroblast like), composition of lining layer. Sublining shows leucocytes infiltrate and high endothelial venules with increased adhesion-molecule expression facilitating recruitment of leucocytes to inflamed synovium, Erosive interface between pannus and cartilage / bone is shown with high level expression of matrix metalloporteinases. Pannus is histologically distinct from other regions of the synovium and shows phases of progression. Initially, there is penetration of the cartilage by synovial pannus composed of mononuclear cells and fibroblasts. This tissue invades and destroys adjacent cartilage and bone. The pannus consists of both type A and type B synoviocytes and plasma cells. The interface between pannus and cartilage is occupied predominantly by activated macrophages and synovial fibroblasts (type B synoviocytes ) that have
anchorage-independent proliferation and loss of contact inhibition, which are phenotypes shown by transformed cells. It also expresses matrix metalloproteinases and cathepsins. IL-1 and TNF-α stimulate the expression of adhesion molecules on endothelial cells and increase the recruitment of neutrophils into the joints. Neutrophils release elastase and proteases, which degrade proteoglycan in the superficial layer of cartilage. The depletion of proteoglycan enables immune complexes to precipitate in the superficial layer of collagens and exposes chondrocytes (Cachren et al., 1990).

![Joint damage in Rheumatoid Arthritis](image)

**Figure 2.5: Joint damage in Rheumatoid Arthritis**

**Common complications of rheumatoid arthritis include the following:**

Peripheral neuropathy and carpal tunnel syndrome: This condition results from damage to nerves, most often those in the hands and feet. It can result in tingling, numbness, or burning.

**Anemia:** This is a low level of hemoglobin, a protein in the blood that carries essential oxygen to cells and tissues. Symptoms include weakness, low energy, pallor, and shortness of breath.

**Scleritis:** This is an inflammation of the blood vessels in the eye that can damage the eyes and impair vision.
Infections: People with rheumatoid arthritis have a higher risk for infections. This is due partly to the abnormal immune system in rheumatoid arthritis and partly to the use of immune-suppressing medications for treatment.

Digestive tract problems: Many people experience stomach and intestinal distress. Again, this is more often a side effect of medications used to treat rheumatoid arthritis.

Osteoporosis: Osteoporosis is more common in women with rheumatoid arthritis than in women in general. The hip is particularly affected. The risk for osteoporosis also appears to be higher than average in men with rheumatoid arthritis who are older than 60 years.

Lung disease: Certain conditions involving inflammation of the lungs seem to be more common in people with rheumatoid arthritis than in the general population. However, a definite link between cigarette smoking and rheumatoid arthritis may at least partly account for this finding. Cigarette smoking, in any case, may increase the severity of the disease.

Heart disease: Rheumatoid arthritis can affect the blood vessels and may increase the risk for coronary heart disease.

Sjogren syndrome: This is another autoimmune rheumatic disease, like rheumatoid arthritis. It causes extreme dryness of certain body tissues, especially the eyes and mouth. Dryness of the eyes is most common in people with rheumatoid arthritis.

Felty syndrome: This condition combines enlargement of the spleen with impairment of the immune system (low white blood cell count), leading to recurrent bacterial infections. This syndrome sometimes responds to DMARD therapy.

Lymphoma and other cancers: The risk for lymphoma, a cancer of the lymph nodes, is higher than normal in people with rheumatoid arthritis. This is thought to be a result of abnormalities in the immune system. Other cancers that may be more common in people with rheumatoid arthritis include prostate and lung cancers.
**Macrophage activation syndrome**: This is a life-threatening complication of rheumatoid arthritis and requires immediate treatment. Symptoms include persistent fever, weakness, drowsiness, and lethargy. The most common causes of premature death in people with rheumatoid arthritis are infection, vasculitis, and poor nutrition.

**Laboratory tests**

Examinations, laboratory Tests and imaging findings associated with RA (Edwards et al., 2004) are shown in table 2.1.

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Associated findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein</td>
<td>Typically increased to &gt;0.7 picograms per mL; may be used to monitor disease course.</td>
</tr>
<tr>
<td>ESR</td>
<td>Often increased to &gt;30 mm per hour; may be used to monitor disease course.</td>
</tr>
<tr>
<td>Hemoglobin/hematocrit*</td>
<td>Slightly decreased; hemoglobin averages around 10 gm per dL; normochromic anemia, also may be normocytic or microcytic.</td>
</tr>
<tr>
<td>Liver function</td>
<td>Normal or slightly elevated alkaline phosphatase</td>
</tr>
<tr>
<td>Platelets</td>
<td>Usually increased</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td>May be normal or show osteopenia or erosions near joint spaces in early disease; wrist and ankle films are useful as baselines for comparison with future studies.</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>Negative in 30 percent of patients early in illness; if initially negative, can repeat six to 12 months after disease onset; can be positive in numerous other processes (e.g., lupus; scleroderma; neoplastic disease; various viral, parasitic, or bacterial infections); not an accurate measure of disease progression.</td>
</tr>
<tr>
<td>White blood count</td>
<td>May be increased</td>
</tr>
<tr>
<td>Test</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Anticyclic citrullinated peptide antibody</td>
<td>Tends to correlate well with disease progression; increases sensitivity when used in combination with rheumatoid factor; more specific than rheumatoid factor (90 versus 80 percent); not readily available in many laboratories.</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Limited value as a screening study for RA</td>
</tr>
<tr>
<td>Complement levels</td>
<td>Normal or elevated</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Elevated alpha-1 and alpha-2 globulins possible.</td>
</tr>
<tr>
<td>Joint fluid evaluation</td>
<td>if an affected joint can be tapped and diagnosis is uncertain; straw-colored fluid with fibrin flecks often seen; fluid may clot at room temperature; 5,000 to 25,000 white blood cells per mm^3 with 85 percent polymorphonuclear leukocytes a common finding; in rheumatoid arthritis, cultures are negative, there are no crystals, and fluid glucose level typically is low.</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Microscopic hematuria or proteinuria may be present in many connective tissue diseases.</td>
</tr>
<tr>
<td>X-rays</td>
<td>Early in rheumatoid arthritis, the x-ray may be normal or show only soft tissue swelling, but damage can still be occurring. Over time, the usual finding is erosion of the bony part of the joint. These changes are distinguishable from changes seen with other types of arthritis such as osteoarthritis.</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Ultrasound uses high-frequency sound waves to take pictures of structures inside the body. It can be used to examine and to detect abnormal collections of fluid (effusions, which cause swelling) in the soft tissues around joints that are not easily accessible (such as hip joints or shoulder joints in obese patients).</td>
</tr>
</tbody>
</table>
Bone scanning: A special picture of the entire skeleton is taken after a harmless radioactive isotope is injected into a vein. Diseased or damaged bone takes up the radioisotope in a different way than healthy bone and gives a characteristic picture. This technique may be used to detect inflammatory changes in bone.

Arthroscopy A small scope, a long narrow tube with a light and a camera on the end, is used to examine the inside of the joint. The scope is inserted through a small incision in the skin. The camera transmits pictures to a video monitor, to detect signs of rheumatoid arthritis or other joint disease.

Table 2.1: Laboratory tests and finding associated with Rheumatoid arthritis

2.2.4 Prevention and cure of Rheumatoid Arthritis

There is no known cure for rheumatoid arthritis. To date, the goal of treatment in rheumatoid arthritis is to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Early medical intervention has been shown to be important in improving outcomes. Aggressive management can improve function, stop damage to joints as seen on x-rays, and prevent work disability. Optimal treatment for the disease involves a combination of medications, rest, joint strengthening exercises, joint protection, and patient (and family) education. Treatment is customized according to many factors such as disease activity, types of joints involved, general health, age, and patient occupation (Lippincott, 2003; Moeser et al., 1991).

Rheumatoid arthritis is a progressive inflammatory disease. This means that unless the inflammation is stopped or slowed, the condition will continue to get worse in most people. Although rheumatoid arthritis does occasionally go into remission without treatment, this is rare. The best medical care combines medication and nondrug approaches.
Nondrug approaches include the following:

- Physical therapy helps preserve and improve range of motion, increase muscle strength, and reduce pain.
- Hydrotherapy involves exercising or relaxing in warm water. Being in water reduces the weight on joints. The warmth relaxes muscles and helps relieve pain.
- Relaxation therapy teaches techniques for releasing muscle tension, which helps relieve pain.
- Both heat and cold treatments can relieve pain and reduce inflammation. Some people’s pain responds better to heat and others to cold. Ultrasound, microwaves, warm wax, or moist compresses can apply heat. Most of these are done in the medical office, although moist compresses can be applied at home. Cold can be applied with ice packs at home.
- Occupational therapy teaches the ways to use body efficiently to reduce stress on joints. It also can help to decrease tension on the joints through the use of specially designed splints.
- Prosorba column: This is not a drug but a medical device. It filters antibodies linked to rheumatoid arthritis out of the blood. This procedure is available only in some medical centers and generally is used only for very severe rheumatoid arthritis.
- In some cases, reconstructive surgery and/or joint replacement operations provide the best outcome.

Drug approaches include a variety of medications used alone or in combinations.

- **First-line medication**
  Acetylsalicylate (aspirin), naproxen, ibuprofen, are examples of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are medications that can reduce tissue inflammation, pain, and swelling. Aspirin, in doses higher than those used in
treating headaches and fever, is an effective anti-inflammatory medication for rheumatoid arthritis. Corticosteroid medications can be given orally or injected directly into tissues and joints. They are more potent than NSAIDs in reducing inflammation and in restoring joint mobility and function. Corticosteroids are useful for short periods during severe flares of disease activity or when the disease is not responding to NSAIDs. However, corticosteroids can have serious side effects, especially when given in high doses for long periods of time. These side effects include weight gain, facial puffiness, thinning of the skin and bone, easy bruising, cataracts, risk of infection, muscle wasting, and destruction of large joints, such as the hips. Abruptly discontinuing corticosteroids can lead to flares of the disease or other symptoms of corticosteroid withdrawal and is discouraged. Thinning of the bones due to osteoporosis may be prevented by calcium and vitamin D supplements.

- **Second-line medication**

While first-line medications (NSAIDs and corticosteroids) can relieve joint inflammation and pain, they do not necessarily prevent joint destruction or deformity. Rheumatoid arthritis requires medications other than NSAIDs and corticosteroids to stop progressive damage to cartilage, bone, and adjacent soft tissues. These second-line or slow-acting or disease-modifying antirheumatic drugs (DMARDs) may take weeks to months to become effective. They are used for long periods of time, even years, at varying doses. DMARD includes Sulfasalazine, Hydroxychloroquine, D-penicillamine, Immunosuppressant i.e. methotrexate azathioprine and Gold salts.

**Biological agents**

**Tumor necrotic factor- (TNF) blockers;**

**Infliximab** (Remicade): It is known as a "chimeric monoclonal antibody". The drug reduces the amount of active TNFα (tumour necrosis factor alpha) in the body by binding to it and preventing it from signaling the receptors for TNF α on the surface of cells.
Etanercept (Enbrel): It is a human recombinant, soluble tumor necrosis factor-alpha (TNF α) receptor. It is a small protein that binds TNF α and decreases its role in inflammatory diseases such as rheumatoid arthritis. It is generally tolerated well than infliximab and it does not seem to cause reactivation of tuberculosis. There are two types of TNF receptors: those found embedded in white blood cells that respond to TNF by releasing other cytokines, and soluble TNF receptors which are used to deactivate TNF and blunt the immune response. Etanercept mimics the inhibitory effects of naturally occurring soluble TNF receptors.

Adalimumab (Humira): It is the third TNF antagonist. Like infliximab and etanercept, adalimumab binds to TNF α, preventing it from activating TNF receptors; adalimumab was constructed from a fully human monoclonal antibody.

Interleukin-1 receptor antagonists
Rhuil-1ra is the exogenous recombinant Il-1ra whose clinical trial results are promising. Anakinra is an IL-1 receptor antagonist, often used as a DMARD. Abatacept is the first selective modulator of a costimulatory signal required for full T cell activation, for the treatment of rheumatoid arthritis.

Surgery
Some people with rheumatoid arthritis need several operations over time. Examples include removal of damaged synovium (synovectomy), tendon repairs, and replacement of badly damaged joints, especially the knees or hips. Some people with rheumatoid arthritis have involvement of the vertebrae of the neck (cervical spine). This has the potential for compressing the spinal cord and causing serious consequences in the nervous system. A variety of complementary approaches may be effective in relieving pain. These include acupuncture and massage (Arend et al., 1997).

Rheumatoid arthritis is not fatal, but complications of the disease shorten life span by a few years in some individuals. Although generally rheumatoid arthritis cannot be cured, the disease gradually becomes less aggressive and symptoms may even improve. However, any damage to joints and ligaments and any deformities that have occurred are permanent. Rheumatoid arthritis can affect parts of the body other than the joints.
Gene Therapy

Gene therapy, the transfer of genes to patients for therapeutic purposes, is being used in the treatment of RA for a number of reasons. First, current steroidal and non-steroidal treatments have limited efficacy and a high incidence of side effects. Second, biologic agents must be administered subcutaneously or intravenously at least once weekly, and disease symptoms return when treatment is stopped. Furthermore, susceptibility to infection may increase when using immunomodulatory molecules such as TNF and IL-1 systemically in RA. Finally, local injection of biologic agents into joint spaces is followed by rapid clearance of these recombinant proteins from the synovial fluid. In this condition, daily injections may be indicated. When a gene that encodes therapeutic proteins is administered into the affected joint, it enables the joint itself to produce high local levels of these therapeutic mediators that can subsequently inhibit inflammation, synovial proliferation, and cartilage destruction (Robbins et al., 1998; Evans et al., 1999).

Antioxidants

Antioxidants, particularly vitamin E, have received considerable attention in the treatment of human diseases. In rheumatic diseases, active phagocytes and leukocytes migrate into synovial and periarticular tissues causing liberation of active oxygen species that exacerbate and perpetuate the rheumatoid condition (Wittenborg et al., 1998). The risk profile of NSAIDs in long-term treatment of chronic RA makes administration of high-dose vitamin E a possible alternative in the treatment of inflammatory rheumatoid diseases.

Bone Marrow Transplantation

RA may be so severe that it may require immuno suppression to save the patient’s life or vital organ function. One major limiting factor in such immunosuppression therapy is the dangerous hematoablation that can occur at the same time. It is now possible to give supralethal doses of hematoimmunoablative drugs (eg, cyclophosphamide) and to rescue the patient by using hemato poietic stem cell transplantation (Tyndall et al., 1999).
The mechanism of efficacy of stem cell transplantation in RA is unknown. It may be attributed either to elimination of the putative auto aggressive immune cells or resetting of the immune system during the process of transplantation (Snowdene et al., 1996).

**Natural approaches**

Various phytochemical from herbal plant show beneficial effect in rheumatoid arthritis. These include flavonoids, terpenes, quinones, catechins, alkaloids, polyphenols, anthocyanins and anthoxanthins, all of which are known to have anti-inflammatory effects. Boswellic acid, berberine, celastrol, curcumin, eugenol and guggulsterone have antiarthritic activity (Kimmatkar et al., 2003: Sethi et al., 2007).
2.3 Diabetes

There are many diseases that are caused due to genetical disorders, and is one of the cause for Diabetes Mellitus. Diabetes is a disorder of metabolism - the way our bodies use digested food for growth and energy. Most of the food eaten by human being is broken down by the digestive juices into a simple sugar called glucose. Glucose is the main source of fuel for the body (Pittas, 2003). After digestion, the glucose passes into bloodstream where it is available for body cells to use for growth and energy. For the glucose to get into the cells, insulin must be present. Insulin is a hormone produced by the pancreas, a large gland near the stomach. When we eat, the pancreas is supposed to automatically produce the right amount of insulin to move the glucose from our blood into our cells. If body doesn’t make enough insulin or the insulin doesn’t work right, the sugar cannot get into the cells. It stays in the blood. This makes high levels of glucose (or sugar) in the blood (hyperglycemia). As a result, glucose builds up in the blood, overflows into the urine, and passes out of the body (glucosuria). Thus, the body loses its main source of fuel even though the blood contains large amounts of glucose. Thus Diabetes is a chronic condition that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin. According to American Diabetes Association Expert Committee, Diabetes mellitus has been defined as a group of metabolic diseases characterized by hyperglycemia, altered metabolism of lipids, carbohydrates & proteins resulting from defects in insulin secretion, insulin action or both (ADA, 2004). The chronic hyperglycemia is associated with long damage, dysfunction & failure of various organs especially the eyes, kidneys, nerves, heart & blood vessels thus covering a wide range of heterogeneous disease (Williams, 2002).

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to the pancreas may produce little insulin. In other cases, the pancreas may produce some insulin, but the cells do not respond to it. Diabetes mellitus is characterized by hyperglycemia, glycosuria, hyperlipemia, negative nitrogen balance and sometimes ketonemia (Tripathi, 2003).


### 2.3.1 Classification of diabetes mellitus

#### Previous classification:

- **Type I**: Juvenile onset diabetes/insulin dependent diabetes mellitus
- **Type II**: Adult onset diabetes/non-insulin dependent diabetes mellitus

#### Now classified as:

- **Type I**: Immune mediated (could be in children with a more rapid onset (classic) or adults with a slower onset 'late autoimmune diabetes of adults')
- **Type II**: Insulin resistant
- Gestational diabetes mellitus
- Other specific types – e.g. certain genetic defects; drug induced; (Pickup, 1991).

**Type I diabetes (Also known as IDDM or juvenile diabetes):** It is characterized by severe lack of insulin due to the destruction of most or all of the beta cells in the islets of Langerhans by an autoimmune process, usually leading to absolute insulin deficiency. The onset is usually acute, developing over a period of a few days to weeks. Over ninety five percent of persons with type I diabetes mellitus develop the disease before the age of twenty five and most often between the ages of ten and sixteen, with an equal incidence in both sexes and an increased prevalence in the white population. Type I diabetes is invariably treated with insulin.

**Type II diabetes mellitus (Also known as NIDDM or adult-onset):** Insulin resistance in peripheral tissue and an insulin secretory defect of the beta cell of pancreas, so that less glucose is produced, and to an impairment of insulin’s ability to stimulate the uptake of glucose in muscles and other tissues. The cause of this insulin resistance has not yet been fully established, but may involve defects in the action of insulin after it has bound to the insulin receptor on the surface of cells. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise (Gary et al., 2003; Rang and dale 2003).

**Gestational diabetes:** Occur during pregnancy, sensitivity to insulin decreases (placental hormones affect glucose tolerance). Beta cells may not be able to meet
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this increased need for insulin gestational diabetes. This increases subsequent risk of developing type II diabetes. Increased risk for perinatal mortality and neonatal morbidity.

**Other types of diabetes mellitus**

Specific genetic/molecular defects have been identified in type II diabetes:

1) Genetic defects of function of beta cell e.g. Hepatic nuclear factor 4 alpha – autosomal dominant condition of impaired insulin secretion; early onset and slowly progressive; type I (mature onset diabetes of the young). e.g. Mutation of mitochondrial DNA.

2) Genetic defects in the action of insulin: e.g. insulin receptor – (severe insulin resistance) lipoatrophic diabetes

3) Endocrine disorders

   - Diseases of the pancreas e.g. pancreatitis, neoplasia, cystic fibrosis, haemochromatosis.
   - Endocrinopathies e.g. acromegaly, Cushing’s syndrome, hyperthyroidism,
   - Pheochromocytoma.

4) Drug/chemical induced: e.g. vacor, pentamidine, glucocorticoids, thiazides, dilantin

5) Infection: e.g. congenital rubella, cytomegalovirus

6) Immune mediated (uncommon): e.g. Stiff man syndrome, anti-insulin receptor antibodies.

**2.3.2 Causes of Diabetes**

   - Heredity i.e. family history of late onset diabetes
   - Obesity i.e. over weight
   - Lack of physical activity i.e. sedentary life style
   - Women with prior gestational diabetes
   - Stress and Strain (Norris et al., 2001).

**Symptoms of diabetes** (Shojania et al., 2006)

a) Symptoms of type I diabetes may include

   - Increased thirst and urination
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- Frequent urination
- Blurred vision
- Feeling very hungry
- Weight loss in spite of increased eating

b) Symptoms of type II diabetes may include
- Feeling tired or illness
- Frequent urination (especially at night)
- Unusual thirst
- Weight loss
- Blurred vision
- Frequent infections
- Slow healing of sores.
- Having dry, itchy skin
- Having tingling in the feet.

Complications occur in diabetes:

Acute Complications in Type – I Diabetes (IDDM)
- Due to illness or fever, insulin requirement increases if additional requirement of insulin is not met with, a diabetic coma can develop.
- Diabetic Ketoacidosis – Appearance of large amount of glucose along with “Ketone” bodies in urine.

Acute Complications in Type – II Diabetes (NIDDM)
- Dehydration coma – Loss of excessive amounts of water and salt.
- Skin problems.

Long Term Complications
- **Eyes:** Progressive loss of vision, leading to blindness, diabetes is among the three common causes of blindness today.
- **Heart:** Diabetics are very prone to developing high blood pressure.
- **Blood Vessels and Circulation:** The arteries may develop fat deposits hindering flow of blood, affecting the blood supply to extreme parts of limbs.
An injury of such limbs may develop gangrene, which may lead to an amputation.

- **Kidneys**: More susceptible to infections of the urinary bladder and kidneys. It may also lead to failure of kidney functions.
- **Nervous System**: Diabetes affects the nerves leading to loss of sensation. In contrast certain diabetics may suffer from tingling or burning sensation in extreme parts of limbs (Zimmet et al., 2001)

### 2.3.3 Prevention and cure of diabetes mellitus:

It may not be possible to prevent diabetes in all cases but even delay in its onset is an achievement. First step is the identification of high-risk groups. These high-risk individuals follow.

- Regular exercise to maintain normal body weight
- Obese persons should undergo diet control and exercise to reduce weight.
- Avoid fast food and take original Indian lacto vegetarian food
- Avoid stressful life.
- Meditation and yoga can also help.

**Drugs used in diabetes (Oral Hypoglycemic agents):**

1) Sulphonylureas: Gibenclamide, Tolbutamide, Chlorpropamide, Tolazamide Glipizide, Gliclazide
2) Biguanides: Metformin, Phenformin
3) α- Glucosidase inhibitors: Acarbose, Miglitol, Voglibose
4) Thiazolidinedione derivatives: Troglitazone, Ciglitazone
5) Inhibitors or gluconeogenesis : Dichloroacetic acid (DCA)
6) Inhibitors of lypolysis: Acipimox (Nicotinic acid analogue)
7) Fatty acid oxidation: Tetrahydecylglycidic acid (TDGA)
2.4 Inflammation

Inflammation is the body’s natural response to being injured. It is characterized by redness, swelling, heat and pain. Inflammation can prevent the normal use of the joint and cause it to lose the ability to function properly. The key to reducing the pain of arthritis and progression is controlling the inflammation that precedes the condition. Drugs developed to manage arthritis normally work by curbing the inflammatory process (Vane et al., 1998).

2.4.1 Principles of inflammation

Inflammation is defined in Webster’s Medical Dictionary as “A local response to cellular injury that is marked by capillary dilatation, leukocyte infiltration, redness, heat, pain, swelling, and often loss of function and that serves as a mechanism initiating the elimination of noxious agents and damaged tissue”.

A human or animal must defend itself against multitude of different pathogens including viruses, bacteria, fungi, and protozoan and metazoan parasites as well as tumors and a number of various harmful agents which are capable to derange its homeostasis. For this, a plenty of effectors mechanisms capable of defending the body against such antigens and agents have developed and these can be mediated by soluble molecules or by cells (Abbas et al., 2009; Anonymous, 1986).

Factors involved in cell damage

There are two categories of factors capable to induce the damage of cells and tissues – endogenous and exogenous (Mackay et al., 2000).

Endogenous damaging factors include immunopathological reactions, and some neurological and genetically disorders.

Exogenous factors can be divided into:

- Mechanical (traumatic injury).
- Physical (extremely low or high temperature, ionizing irradiation, microwaves).
- Chemical (caustic agents, poisons, venoms, genotoxic and proteotoxic compounds).
- Nutritive (deficiency of oxygen, vitamins and basic nutrients).
- Biological (viruses, microorganisms, protozoan and metazoan parasites).
2.4.2 Pathophysiology of inflammation

**Acute inflammation:** It may develop over minutes or hours depending on the type and severity of the tissue damage and generally lasts hours to days. Vascular dilatation, increased vascular permeability and neutrophil activation and migration are interdependent processes and all three are required for the full response. Immediately after the tissue damage has occurred, there may be a brief phase of constriction of arterioles but this is followed within seconds by arteriolar dilatation, which leads to increased blood flow to the area. At much the same time, gaps form between endothelial cells of the capillaries allowing protein-rich plasma to leak into the tissue. The dilated capillaries become engorged with red cells and blood flow slows and then stops. The slowing of blood flow brings neutrophils into contact with the endothelial cells, which have been busy inserting adhesion molecules into their plasma membranes.

As the neutrophils come into contact with the endothelium, adhesion molecules on the neutrophil plasma membrane bind to their complementary receptors on the endothelial cells and become stuck. Activation of the neutrophils plays a role here so that activated neutrophils are more likely to stick. Meanwhile in the tissues, the plasma-derived proteins undergo various changes. Immunoglobulins bind to any causative organisms immobilizing them, and forming immune complexes that further activate complement (classical pathway). *Fibrinogen* is cleaved to form a network of *fibrin* that impedes the movement of fibrin monomers, which polymerize to form pathogenic organisms and provides a framework for the migration of neutrophils (Bainton, 1999).

The increased fluid in the tissue causes an increased flow of lymph to carry immune complexes and antigenic material to the lymph nodes where a specific immune response is initiated over a matter of days. The neutrophils pass through the basement membrane of the endothelium and move along a concentration gradient of chemotactic factors. When they arrive at the site of injury, the activated neutrophils phagocytose necrotic tissue debris and pathogenic organisms. The activation of the neutrophils makes them more efficient at phagocytosis and killing. Opsonization of bacteria by complement and
immunoglobulin renders them more readily phagocytosed. This entire process is orchestrated by a plethora of chemical mediators derived from injured tissues, bacteria, plasma proteins and leucocytes. The most important of these mediators are indicated at their sites of action.

The process of acute inflammation is designed to neutralize injurious agents and to restore the tissue to useful function. There are four main outcomes of acute inflammation if the patient survives: resolution, healing by fibrosis, abscess formation, and progression to chronic inflammation. Three factors determine which of these outcomes occurs:

- The severity of tissue damage
- The capacity of specialized cells within the damaged tissue to divide and replace them, a process termed regeneration
- The type of agent, which has caused the tissue damage.

**Chronic inflammation:** It may result following acute inflammation when an injurious agent persists over a prolonged period causing concomitant tissue destruction, inflammation, organization and repair. Some injurious agents elicit a chronic inflammatory type of response from the outset.

**Exudation and swelling**

**Fluid exudates:** In acute inflammation, the pressure in post capillary venules may overcome the osmotic pressure of plasma proteins. Therefore fluid and low molecular substances have the tendency to penetrate into the surrounding area. The vascular permeability for proteins and some smaller molecules differs from tissue to tissue (Saito et al., 2002).

**Cellular exudates:** Cellular exudate is formed during the second and the third phase of inflammation acute and chronic cellular response.

**Cells participating in inflammation**

1) **Mast cells and basophils**

Mast cells and basophiles play a central role in inflammatory and immediate allergic reactions. They are able to release potent inflammatory mediators, such as histamine, proteases, chemotactic factors. Both mast cells and basophils contain special *cytoplasmic granules* which store mediators of inflammation. The
extra cellular release of the mediators is known as degranulation and may be induced by:

(a) Physical destruction, such as high temperature, mechanical trauma, ionizing irradiation, etc.

(b) Chemical substances, such as toxins, venoms, proteases;

Endogenous mediators, including tissue proteases, cationic proteins derived from eosinophils and neutrophils;

2) **Eosinophils**

The Eosinophil is a terminally differentiated, end-stage leukocyte that resides predominantly in sub mucosal tissue and is recruited to sites of specific immune reactions, including allergic diseases. The mean generation time for eosinophils in the bone marrow is approximately 2-6 days. They mainly settle in the tissue where their number is about one hundred times higher than in the blood. Like other granulocytes, they possess a polymorphous nucleus, although with only two lobes and no nucleolus (Borregaard et al., 1993).

3) **Neutrophils, central cells in acute inflammation**

Neutrophils, which are also known as polymorph nuclear leukocytes (PMN), represent 50 to 60% of the total circulating leukocytes and constitute the “first line of defence” against infectious agents or “nonself” substances that penetrate the body’s physical barriers. Once an inflammatory response is initiated, neutrophils are the first cells to be recruited to sites of infection or injury. Their targets include bacteria, fungi, protozoa, viruses, virally infected cells and tumour cells. Their development in the bone marrow takes about two weeks; during this period, they undergo proliferation and differentiation (Salvemini et al., 1991).

4) **Neutrophil granules**

The neutrophil granules are of major importance for neutrophil function. When referring to phagocytes or leukocytes in general, the term granule is used more often than lysosome. They kill ingested bacteria and, finally, to secrete their contents to regulate various physiological and pathological processes, including inflammation.
5) **Cytokines:**
They are basic regulators of all neutrophil functions. Many of them including haematopoietic growth factors and pyrogens have shown to be potent neutrophil priming agents. Neutrophils also synthesize and secrete small amounts of some cytokines including IL-1, IL-6, IL-8, TNF, and GM-CSF; they may act in an autocrine or paracrine manner. Histamine is a potent inhibitor of neutrophil microbicidal activity (Borregaard et al., 1993)

6) **Macrophages and monocytes:**
Originally, monocytes and macrophages were classified as cells of the reticuloendothelial system – RES proposed the mononuclear phagocyte system – MPS, and monocytes and macrophages became basic cell types of this system. Their development takes in the bone marrow (Rankin et al., 2004).

**Mediators of Inflammation**
There are four major plasma enzyme systems which have an important role in haemostasis and control of inflammation. These are the complement system, the clotting system, the fibrinolytic (plasmin) system and the kinin system.

Inflammatory mediators are soluble, diffusible molecules that act locally at the site of tissue damage and infection, and at more distant sites. They can be divided into exogenous and endogenous mediators. Bacterial products and toxins can act as *exogenous mediators* of inflammation. Notable among these is *endotoxin*. The immune system of higher organisms has probably evolved in a veritable sea of endotoxin, so it is perhaps not surprising that this substance evokes powerful responses (Willis et al., 1996). Endogenous mediators are produced from within the (innate and adaptive) immune system itself, as well as other systems (McMahon et al., 2006; Zimmerman, et al., 1992)

**Other mediators are:**
- Mononuclear phagocytes
- Thromboxanes A
- Leukotrienes
- Lipoxins
- platelet-activating factors (PAFs)
Symptoms of inflammation
Inflammation is characterized by:

- Redness
- Swollen joint that is warm to touch
- Joint pain
- Joint stiffness
- Loss of joint function

Often, only a few of these symptoms are present (Nathan et al., 2002).

2.4.3) Prevention and cure of inflammation (Marieb, 1997)

1) Drugs with analgesic but with negligible anti-inflammatory actions
   a) Aniline derivatives: eg. paracetamol

2) Drugs with analgesic and mild to moderate anti-inflammatory actions:
   a) Propionic acid derivatives which include ibuprofen, ketoprofen, Fenoprofen, flurbiprofen
   b) Anthranilic acid derivatives which include mefanemic acid, flufenamic acid
   c) Acryacetic acid derivatives which include fenclofenac, diclofenac

3) Drugs with analgesic and marked inflammatory actions:
   a) Salicylates and its derivatives which include aspirin, sodium salicylates, benorylate etc
   b) Pyrazolon derivatives which include indomethcin, sulindac.

4) Drugs having good anti inflammatory actions:
   a) Corticosteroids
   b) COX 1 and cox 2 inhibitors
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2.5 Hypertension

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Blood pressure is a measurement of the force against the walls of arteries as heart pumps blood through the body. Blood pressure involves two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). Normal blood pressure at rest is within the range of 90-120 mmHg systolic and 60-80 mmHg diastolic. High blood pressure is said to be present if it is persistently at or above 140/90 mmHg (Satoshkar, 1983).

There are usually no symptoms or signs of hypertension, and thus it is called the “silent killer” because it often causes no symptoms for many years, even decades, until it finally damages certain critical organs. Poorly controlled high blood pressure ultimately can cause damage to blood vessels in the eye, thickening of the heart muscle and heart attacks, hardening of the arteries (arteriosclerosis), kidney failure, and strokes.

An elevation of the systolic and/or diastolic blood pressure increases the risk of developing heart (cardiac) disease, kidney (renal) disease, hardening of the arteries (atherosclerosis or arteriosclerosis), cognitive impairment, dementia eye damage, and stroke (brain damage). These complications of hypertension are often referred to as end-organ damage because damage to these organs is the end result of chronic (long duration) high blood pressure (Hamilton et al., 1964; Dehlof et al., 1991)
2.5.1 Hypertension can be classified either Essential (Primary) or Secondary (table 2.2)

1) Primary (Essential) hypertension: It is the most common form of hypertension, accounting for 90–95% of all cases of hypertension. Hypertension results from a complex interaction of genes and environmental factors. Numerous common genes with small effects on blood pressure as well as some rare genes with large effects on blood pressure have been identified, but the genetic basis of hypertension is still poorly understood.

Causes of primary hypertension:
- Obesity
- Sodium sensitivity
- Role of rennin enzyme
- Insulin resistance
- Age
- Vitamin D

2) Secondary hypertension: High blood pressure that is caused by another medical condition or medication is called secondary hypertension. Secondary hypertension also results from identifiable causes. With treatment of the underlying cause, secondary hypertension can resolve without the need of antihypertensive medication (O'Brien et al., 2007; Grossman et al., 2012)
• Sleep apnea
• Liquorices consumption
• Tumors
• Cushing syndrome
• Contraction of the aorta.
• kidney diseases or endocrine diseases
• Thyroid disease and acromegaly
• Pregnancy
• Medications such as birth control pills, diet pills, some cold medications, and migraine medications, especially NSAIDs (Motrin/Ibuprofen) and steroids can cause hypertension
• Narrowed artery that supplies blood to the kidney (renal artery stenosis)
• Three types of secondary high blood pressure (hypertension): renal (kidney) hypertension, adrenal gland tumors, and contraction of the aorta (Fig.2.6).

Figure: 2.6 Blood Pressure
2.5.2 Pathophysiology

A diagram (Fig.2.6 and 2.7) explaining factors affecting arterial pressure. In most people with established essential (primary) hypertension, increased resistance to blood flow (total peripheral resistance) accounting for the high pressure while cardiac output remains normal. Some younger people with prehypertension or ‘borderline hypertension’ have high cardiac output, an elevated heart rate and normal peripheral resistance, termed hyperkinetic borderline hypertension (Palatini et al., 2009). These individuals develop the typical features of established essential hypertension in later life as their cardiac output falls and peripheral resistance rises with age. The increased peripheral resistance in established hypertension is mainly attributable to structural narrowing of small arteries and arterioles (Folkow et al. 1982), although a reduction in the number or density of capillaries may also contribute (Struijker et al., 1992).

Hypertension is also associated with decreased peripheral venous compliance (Safar et al., 1997), which may increase venous return, increase cardiac preload and, ultimately, cause diastolic dysfunction. Whether increased active vasoconstriction plays a role in established essential hypertension is unclear.

Pulse pressure (the difference between systolic and diastolic blood pressure is frequently increased in older people with hypertension. Systolic pressure is abnormally high, but diastolic pressure may be normal or low, the condition termed isolated systolic hypertension. The high pulse pressure in elderly people with hypertension or isolated systolic hypertension is explained by increased
arterial stiffness, which typically accompanies aging and may be exacerbated by high blood pressure (Chobanian et al. 2007; Zieman et al., 2005)

2.5.3 Prevention and cure of hypertension

Management of hypertension can be achieved by considering following points:

- Cardiovascular risk assessment
- Lifestyle interventions
- Blood pressure control
- Coexisting conditions
- Fixed-dose combination products
- Monitoring response and altering drug therapy
- Adherence to medicines
- Potential drug effects on blood pressure and interactions

Pharmacological therapy is not an important component of treatment of all patients with hypertension. In stage 1 hypertensive, blood pressure may be adequately controlled by a combination of weight loss (in overweight individuals), restricting sodium intake, increasing aerobic exercise and moderating consumption of alcohol.

Drug therapy:

<table>
<thead>
<tr>
<th>Class Drugs</th>
<th>Name of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Creatine, Captopril, Enalapril, Fosinopril, Lisinopril, Quinapril, Ramipril</td>
</tr>
<tr>
<td>Angiotensin II receptor</td>
<td>Telmisartan, Irbesart, Losartan, Valsartan, Candesartan</td>
</tr>
<tr>
<td>antagonists</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Nifedipine, Diltiazem, Verapamil</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Bendroflumethiazide, Chlortalidone, Hydrochlorothiazide</td>
</tr>
<tr>
<td>Alpha blockers</td>
<td>Prazosin, Terazosin</td>
</tr>
</tbody>
</table>
Chapter 2

Review literature

<table>
<thead>
<tr>
<th>Beta blockers</th>
<th>Atenolol, Labetolol, Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺ ATP channel blocker</td>
<td>Minoxidil, Sodium nitroprusside, Diazoxide</td>
</tr>
</tbody>
</table>

Table 2.3 Classification of Antihypertensive drugs

a) **ACE inhibitors** like captopril, enalapril, and lisinopril decrease the conversion of angiotension I to angiotensin II (AT II). This reduces peripheral vascular resistance and promotes both natriuresis and hyperkalemia, since a reduction in AT II leads to a reduction in aldosterone. ACE also breaks down bradykinin, so inhibiting this enzyme can increase bradykinin levels and cause more vasodilation. ACE inhibitors have been shown to reduce morbidity and their relatively benign side effect profile makes them frequent choices for first-line or monotherapy. Diabetics who do not have a contraindication for this class of drugs should be taking them for renal protective purposes..

b) **Angiotensin receptor blockers (ARB’s)** like losartan and valsartan cause arteriolar vasodilation by blocking the effects of angiotensin II at the angiotensin type I receptor. Since the mechanism is essentially the same as for the ACE inhibitors, the indications and contraindications are the same. The blockade is downstream, so bradykinin is not elevated, and this class of drugs is not associated with a cough (Goodman gilman, 2011; Hebert 1993).

c) **Calcium channel blockers:** such as verapamil, diltiazem, nifedipine and amlodipine block L-type calcium channels and are effective arterial vasodilators. The dihydropyridine agents nifedipine and amlodipine act primarily as vasodilators and have minimal direct effects on the heart. In contrast, verapamil and diltiazem act principally as negative inotropes and negative chronotropes, and thus decrease heart rate, contractility and cardiac conduction speed. Verapamil and diltiazem are synergistic with beta-blockers and the combination can cause severe bradycardia, heart block or pump dysfunction.

d) **Vasodilators:** Direct arterial vasodilators such as minoxidil and hydralazine have relatively limited use. Neither has much effect on venous tone. Minoxidil
appears to increase potassium conductance in vascular smooth muscle, and the resultant hyperpolarization reduces calcium entry. Both drugs can cause reflex tachycardia (particularly minoxidil) and fluid retention. These side effects can be managed with the addition of a beta-blocker and/or a diuretic. Neither drug is effective for sustained periods. They are usually reserved for the short-term treatment of refractory hypertension, especially in patients with renal failure.

e) **Diuretics:** further classified into thiazide diuretics, loop diuretics and potassium-sparing diuretics.

- **Thiazide diuretics:** Such as hydrochlorothiazide and chlorthalidone are among the most commonly used drugs for treating hypertension. They inhibit reabsorption of sodium and chloride in the distal tubule and lose effectiveness when glomerular filtration rate is low. Their initial effects are said to be mediated by decreasing intravascular volume, most untreated hypertensives have contracted intravascular volume. Diuretics cause peripheral vascular resistance to fall through an unknown mechanism.

- **Loop diuretics:** Such as furosemide inhibit the Na/K/Cl co-transporter in the ascending limb of the loop of Henle. Acute intravenous administration of furosemide can cause vasodilation by an unknown mechanism. Loop diuretics are often part of treatment for malignant hypertension and hypertension with hypervolemia (e.g., renal insufficiency). The metabolic derangements produced by these drugs (particularly hypokalemia, and hypocalcemia) can be profound.

- **Potassium-sparing diuretics:** Such as spironolactone, amiloride, and triamterene are not as efficacious as thiazides or loop diuretics in reducing blood pressure, however, they do correct the potassium loss associated with thiazide and loop diuretics. Amiloride and triamterene inhibit the Na/proton exchanger in the distal and collecting tubules. Spironolactone inhibits the Na/K exchanger affected by aldosterone, and it is particularly effective in the face of hyperaldosteronism. If potassium-sparing diuretics
are given to patients on ACE inhibitors, particular care must be taken since both classes cause elevations in serum potassium.

f) **Renin-angiotensin system (RAS) blockers**: Angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin type 1 receptor blockers (ARB’s).

g) **Sympatholytics**: They are further classified into beta-blockers, mixed alpha and beta-blockers, alpha blockers and central sympatholytics.

- **Alpha-1 adrenergic blockers**: Such as prazosin, terazosin and doxazosin are effective at reducing sympathetic vasoconstriction and thereby reducing vascular resistance. These drugs are also useful for men who have benign prostatic hypertrophy because they can reduce bladder outlet obstruction.

- **Beta adrenergic blockers**: such as propranolol, metoprolol or atenolol are typical first-line agents for treating hypertension. They have negative chronotropic and negative inotropic effects. Unfortunately beta-blockers can elevate triglycerides and reduce HDL. In addition, they can produce glucose intolerance, impotence, and depression.

- **Central sympatholytics**: such as clonidine stimulate central alpha-2 receptors and thereby reduce sympathetic outflow. These drugs are effective in decreasing heart rate, contractility and vasomotor tone; however, they cause sedation and are usually not first line therapies.

- **Mixed alpha and beta antagonists**: such as labetalol and carvedilol block both alpha receptors and beta receptors, so the reduction in blood pressure is usually not associated with reflex tachycardia. Labetalol is a very effective intravenous antihypertensive, but it is less frequently used chronically in its oral form. Carvedilol has had its primary use in the treatment of chronic congestive heart failure.

- **K$^+$ ATP channel blocker**: Sodium nitroprusside breaks down non-enzymatically to form nitric oxide. It is an extremely potent arteriolar and venous dilator that is used intravenously for rapid control of hypertensive crises and for blood pressure control during operations.
Reflex increases in heart rate and contractility usually require treatment with beta blockers.

Other precautions

- As a first principle, one should always couple any chemical therapy with lifestyle modifications (maintaining ideal body weight, engaging in aerobic physical exercise, eating a healthy diet low in saturated and total fats, limiting sodium intake and reducing alcohol intake). Each of these lifestyle modifications has been shown to reduce blood pressure modestly.

- As a second principle, additional risk factors for coronary artery disease and stroke should be aggressively managed in all patients with hypertension. In particular, patients should be counselled on smoking cessation, lipid reduction and diabetic management. When these diseases occur in combination, the probability of end-organ damage goes up significantly and careful management of each of the co-morbidities is all the more important.

- Most antihypertensive medications can be used alone or in combination. Some are used only in combination. Some are preferred over others in certain specific medical situations. And some are not to be used (contraindicated) in other situations.

- High blood pressure (hypertension) in pregnancy can lead to preeclampsia or eclampsia. Pregnant women should be monitored closely by their obstetrician for complications of high blood pressure.

- Lifestyle adjustments in diet and exercise and compliance with medication regimes are important factors in determining the outcome for people with hypertension.

- High salt intake, obesity, lack of regular exercise, excessive alcohol or coffee intake, and smoking may all adversely affect the outlook for the health of an individual with high blood pressure.
Diagnostic tests

<table>
<thead>
<tr>
<th>System</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Microscopic urinalysis, proteinuria, serum BUN (blood urea nitrogen) and/or creatinine</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Serum sodium, potassium, calcium, TSH (thyroid-stimulating hormone)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Fasting blood glucose, total cholesterol, HDL and LDL cholesterol, triglycerides</td>
</tr>
<tr>
<td>Other</td>
<td>Hematocrit, electrocardiogram, and chest radiograph</td>
</tr>
</tbody>
</table>

Table : 2.4 Diagnostic tests for hypertension

Hypertension is diagnosed on the basis of a persistently high blood pressure. Laboratory tests can perform to identify possible causes of secondary hypertension, and to determine whether hypertension has caused damage to the heart, eyes, and kidneys (table.2.5). Additional tests for diabetes and high cholesterol levels are usually performed because these conditions are additional risk factors for the development of heart disease and may require treatment. Serum creatinine is measured to assess for the presence of kidney disease, which can be either the cause or the result of hypertension. Serum creatinine alone may overestimate glomerular filtration rate and (Chobanian et al., 2007). Glomerular filtration rate can also provide a baseline measurement of kidney function that can be used to monitor for side effects of certain antihypertensive drugs on kidney function. A chest X-ray or an echocardiogram may also be performed to look for signs of heart enlargement or damage to the heart (Schiffrin et al., 1992).

Complications

When blood pressure is not well controlled, it may be at risk for:

- Bleeding from the aorta, the large blood vessel that supplies blood to the abdomen, pelvis, and legs
- Chronic kidney disease
• Heart attack and heart failure
• Poor blood supply to the legs
• Stroke
• Problems with vision (Goldstein et al., 2011; Victor et al., 2011)
2.6 Convulsion

Convulsion is also known as epilepsy. The word epilepsy is also known from the Greek as epilepsia, which in turn can be broken into epi- (upon) and lepsis (to take hold of or seizure). Epilepsy is a chronic brain disorder characterized by recurrent derangement of the nervous system due to sudden excessive disorderly discharge from the cerebral neurons (Maiha et al., 2009). Seizures are controlled in nearly 70% of patients with epilepsy, mostly through drugs effect on membrane ion channels or on Gamma amino butyric acidergic (GABA) or glutamatergic transmission (Marjan et al., 2009).

Epilepsy is a group of chronic neurological disorders characterized by sporadic episodes of convulsive seizures, sensory disturbance, and loss of consciousness or all of these symptoms resulting from a brain dysfunction or an abnormal discharge of cerebral neurons (Hema et al., 2009; Banerjeea et al., 2009). Epilepsy is the second most common neurological disorder after stroke. It is estimated that approximately 0.8% of the population is affected by some form of epilepsy. In about 30% of epilepsies, there is an identifiable injury to the brain that triggered the development of epilepsy (symptomatic epilepsies). Another 30% of patients have presumed symptomatic epilepsy (previously called cryptogenic epilepsy) in which some brain pathology causing epilepsy is presumed to exist, but has not been identified using current techniques.

Epileptogenesis refers to the phenomenon in which various kinds of brain insults (e.g., traumatic brain injury, stroke, infection, and prolonged febrile seizure) trigger a cascade of events that eventually culminate in the occurrence of spontaneous seizures. An operational definition of epileptogenesis refers to the period between the insult and the occurrence of the first spontaneous seizure. Seizures (from the Latin sacire, “to take possession of”) are discrete; time limited alteration in brain function including changes in motor activity, autonomic function, consciousness, or sensation that results from an abnormal and excessive electrical discharge of a group of neurons within the brain. It has been shown to affect several brain activities and promote long-term changes in multiple neural systems. This disorder, if untreated, can lead to
impaired intellectual function or death and is typically accompanied by Psychopathological consequences such as lose of self-esteem (Manigauha et al., 2009). Status epilepticus is characterized by repeated episodes of epilepsy without the patient having recovered from the previous attack (Panda et al., 2010).

2.6.1 Classification of Seizures

Seizures are classified according to their clinical features and patterns seen on the EEG. Epileptic seizures are divided into two broad categories based on the symptoms and EEG findings observed at the outset of the seizure. If the initial onset indicates involvement of both sides of the brain, the seizures are referred to as generalized seizures and if involvement of only a localized area of the brain, they are referred to as partial seizures.

1. Partial Seizure (Seizure Beginning Locally)

Partial seizures happen when the disturbance occurs in just one part of the brain. With these seizures, the activity can start in one place in the brain, and then move to another, or it could just stay in the one area. These may produce relatively simple symptoms without loss of consciousnesses, such as involuntary muscle contractions, abnormal sensory experiences or autonomic discharge or they may cause more complex effects on consciousness, mood and often termed psychomotor epilepsy (Rang and dale, 2005).

a. Simple partial seizure
b. Complex partial seizure
c. Partial seizure evolving to secondary generalized seizure

a) Simple partial seizures

They are remarkably different from person to person, depending on the part of the brain where they begin. The patient does not lose consciousness, and therefore is able to tell what happened, but the experience may be so strange that he may not be able to express himself properly. What happens is dependent on the location of the affected area. In simple partial seizures, electrical discharges begin in a small area of the brain and remain confined to that area.
Because only a small area of the brain is affected, symptoms are related to the function controlled by that area. For example, if the small area of the brain that controls the right arm’s movements (in the left frontal lobe) is affected, the right arm may begin to shake and jerk. A simple partial seizure may progress to a complex partial seizure. The sensory seizures these cause changes in any one of the senses. There might be feelings of tingling, pins and needles, cold or heat, or numbness of a limb. Sometimes there may be strange feelings with visual signs, or hearing or smelling sensations. The psychic symptoms may consist of changes in mood, memory, or thought (thinking). There may be distorted perceptions (time, space, or person) or problems with language.

**b) Complex partial seizures**

Complex partial seizures generally last thirty seconds to two minutes and are also followed by a short period of confusion or impairment (typically fifteen minutes). Here the patient has impaired consciousness, there is no complete loss of consciousness, person is slightly aware of what is going on, but cannot respond to anything, neither can change behavior during an attack. There is an aura, a strange feeling in the stomach rising up to the throat and head, or a sensation of light, smell, sound or taste (Snead et al., 1996). Sometimes the seizure occurs with hallucinations or with psychomotor symptoms such as automatisms, automatic movements, e.g., chewing, lips smacking, or repeated aimless movements. During such an automatism the patient may become aggressive and violent when restrained. There is a slow recovery after a complex partial seizure, with a period of confusion. After the attack there is complete amnesia of it. These seizures were previously called psychomotor seizures, and as the localization of the abnormal discharge is often in the temporal lobe, the epilepsy is often called temporal lobe epilepsy.

**c) Partial seizures secondary generalized**

If the seizure starts off as a partial seizure, then spreads to include the entire brain, it is referred to as a partial seizure secondarily generalized. This means it started as a partial seizure then became a generalized seizure.
2. Generalized Seizure (Bilaterally Symmetrical and Without Local Onset)

Generalized seizures are produced by electrical impulses from throughout the entire brain, once initiated; it spreads quickly into the entire or at least the greater part of the brain. The primary generalized seizures are characterized by a complete loss of consciousness and the absence of an aura. They come on suddenly and unexpectedly, and if the patients fall, they may injure themselves. The generalized seizures consist of six different seizure types, of which the primary generalized tonic-clonic seizure (GTCS) is the most common.

A. Absence seizures (petit mal seizure)

Absence seizures (also called petit mal (little illness) seizures because they occurred so frequently) are lapses of awareness, sometimes with staring; those begin and end abruptly, lasting only a few seconds. More common in children than in adults, absence seizures almost always start between ages four and twelve years, and rarely do they begin after age twenty.

Absence seizures are characterized by a brief impairment of consciousness, which usually lasts no more than a few seconds. They do not produce the convulsions and other dramatic symptoms of tonic-clonic seizures. A person does not fall down, collapse, or move jerkily. Instead, the person has episodes of staring with fluttering eyelids and sometimes twitching facial muscles. The person is completely unaware of the surroundings. The person abruptly stops activity and resumes it just as abruptly, experiencing no after-effects and not knowing that a seizure has occurred.

Absence seizures are frequently so brief that they escape detection, even if the child is experiencing 50 to 100 attacks daily. They may occur for several months. Absence seizures are accompanied by brief myoclonic jerking of the eyelids or facial muscles, or by variable loss of muscle tone. The absence attack is always associated with the strikingly typical EEG abnormality of spike and slow wave discharges, usually at a frequency of 3Hz. Absence seizures are often confused with complex partial seizures. This is an unfortunate mistake because the drugs that prevent absence seizures have little or no effect on complex partial
seizures. Conversely, the most effective drugs for complex partial seizures are either ineffective against or increase the frequency of absence seizures.

**B. Myoclonic seizures:**

Myoclonic seizures are rapid, brief contractions of bodily muscles, which usually occur at the same time on both sides of the body. Occasionally, they involve one arm or a foot. People usually think of them as sudden jerks or clumsiness. A variant of the experience, common to many people who do not have epilepsy, is the sudden jerk of a foot during sleep. The pathogenesis of myoclonic seizures is probably very similar to that of clonic seizures which essentially consist of repetitive myoclonic jerks. There may be symmetrical, shock-like contractions of the limbs, which may or may not be followed by loss of consciousness.

**Atonic seizures,** in which there is momentary loss of tone in the muscles of the limbs, leading to sudden falling to the ground or dropping of the head. The pattern is most often seen in children who have suffered injury to the brain, through lack of oxygen at birth, meningitis in infancy, etc. Atonic seizures occur primarily in children. They are brief, but they cause the child to collapse to the ground, increasing the risk of injury.

**C. Clonic seizures**

These seizures are generalized seizures, where the tonic component is not present, only repetitive clonic jerks (clonic jerks are repetitive). When the frequency diminishes the amplitude of the jerks do not.

**D. Tonic seizures**

Tonic seizures are sudden sustained muscle contractions, fixing the limbs in some strained position. There is immediate loss of consciousness. Often there is a deviation of the eyes and head towards one side, sometimes rotation of the whole body. They are seen mainly in paediatric practice.

**E. Generalized Tonic Clonic Seizures (GTCS)**

Generalized tonic clonic seizures (grand mal seizures) are the most common and best known type of generalized seizure. Generalized seizures happen when the electrical disturbance sweeps through the whole brain at once, causing loss of consciousness, falls, and convulsions. They begin with stiffening
of the limbs (the tonic phase), followed by jerking of the limbs and face (the clonic phase). During the tonic phase, breathing may decrease or cease altogether, producing cyanosis (blueing) of the lips, nail beds, and face. Breathing typically returns during the clonic (jerking) phase, but it may be irregular. This clonic phase usually lasts less than a minute. Some people experience only the tonic, or stiffening phase of the seizure; others exhibit only the clonic or jerking movements; still others may have a tonic-clonic-tonic pattern. Here the whole brain is affecting from the beginning. There is a cry and loss of consciousness, arms flex up then extend and remain rigid (the tonic phase) for a few seconds. A series of jerking movements take place (the clonic phase) as muscles contract and relax together. Incontinence may occur as a result of the seizure. The tongue or inside of the mouth may be bitten during the episode; breathing afterwards may be noisy and appear to be labored. Following the seizure, the patient will be lethargic, possibly confused, and want to sleep. Headache sometimes occurs. Full recovery takes minutes to hours, depending on the individual (Dekker et al., 2006).

F. Infantile spasms

Infantile spasms are an epileptic syndrome and not a seizure type. The attacks, although sometimes fragmentary, are most often bilateral and are included for pragmatic purposes with the generalized seizures. These attacks are most often characterized clinically by brief, recurrent myoclonic jerks of the body with sudden flexion or extension of the body and limbs; the forms of infantile spasms are, however, quite heterogeneous. 90% of affected patients have their first attack before the age of one year. Most patients are mentally retarded, presumably from the same cause as the spasms. The cause is unknown in many patients, but such widely disparate disorders as infection, kernicterus, tuberous sclerosis and hypoglycemia have been implicated. In some cases, the EEG is characteristic. Drugs used to treat infantile spasms are effective only in some patients; there is little evidence that the mental retardation is alleviated by therapy, even when the attacks disappear (Olubunmi et al., 2006).
2.6.2 Causes of Epilepsy
Epilepsies constitute a large group of neurological diseases with an incidence of 0.5–1% in the general population (Shindikar et al., 2006). Most commonly, seizures disorders begin in early childhood or in late adulthood. Seizures starting before age 2 are usually caused by high fevers or metabolic disorders, such as abnormal blood levels of sugar (glucose), calcium, magnesium, vitamin B₆, or sodium. If the seizures recur, the cause is likely to be a hereditary brain disorder (such as nocturnal frontal lobe epilepsy). The type of seizure depends on the site of the focus in the brain. Epileptic attack can be caused by biochemical insults to the brain, such as hypoglycaemia, anoxia, hypocalcaemia, hyperventilation, water intoxication and sudden withdrawal of certain drugs such as barbiturates or alcohol. Epilepsy can also be caused by previous active pathology, such as birth trauma to the brain, during or following meningitis, trauma to the skull and brain later in life, cerebral abscesses, cerebral infarction, cerebral haemorrhage or subarachnoid haemorrhage (Bienvenu et al., 2006). Other causes included head injury with/without intracranial haemorrhage, central nervous system and systemic infections, and other causes of dementia (Lim at al., 2004).

2.6.3 Pathophysiology of Epilepsy
Seizure activity in the brain is thought to be initiated by a preponderance of excitatory over inhibitory postsynaptic potentials (EPSP, IPSP), resulting in depolarization of nerve cell membranes. Such a depolarization may appear on the EEG as an interictal spike, an initial spike component, or an abrupt depolarization with superimposed high-frequency action potentials paroxysmal depolarization shift. The synchronous discharges of large numbers of neurons result in an epileptic seizure. Normal membrane conductance and inhibitory synaptic currents break down, and excess excitability spreads, either locally to produce a focal seizure or more widely to produce a generalized seizure. The clinical manifestations depend on the site of the focus, the degree of
irritability of the surrounding area of the brain, and the intensity of the impulse (Porter, 2007; Rogers, 2008).

Several physiological mechanism continuous discharges and the development of hypersynchronous discharge in brain areas. Interneurones for example, release the neurotransmitter GABA. Attachment of GABA to the postsynaptic receptor causes an inhibitory (that is hyperpolarizing) postsynaptic potential (IPSP), which counteract the development of postsynaptic action potential. Hyperpolarization also inhibits the occurrence of burst. Glutamate, an excitatory neurotransmitter activates receptor to increases the production of burst of neurons. In absence epilepsy, for example generalized cortical synchronization of spike – wave complexes appears on the EEG with a typical frequency 3Hz thalamic neurons normally discharge to cortical neurons continuously. This regularity results from a balance between GABAergic inhibition and voltage dependent sodium channel, low threshold the T-type calcium channel. In absenc epilepsy latter current is increased and acts as pace maker for the 3Hz rhythmic spike- wave pattern (Meldrum et al. 1988).

**Role of neurotransmitter in Epilepsy**

The major amino acid neurotransmitters in the brain are GABA, an inhibitory transmitter and glutamic acid, an excitatory transmitter. GABA is widely distributed in the mammalian brain. While it is evident that a reduction in GABAergic activity is associated with seizures, and most anticonvulsant drugs either directly or indirectly facilitate GABAergic transmission. The GABAergic system has long been implicated in epilepsy with defects in GABA neurotransmission being linked to epilepsy in both experimental animal models and human syndromes. However, to date, no human epileptic syndromes may be the directly attribute to an altered GABAergic system. The observed defects in GABA neurotransmission in human epileptic syndromes may be the indirect result of a brain besieged by seizures. There is now evidence that many epilepsy-associated genes participate in secondary cellular plasticity during brain development, which is likely to influence
downstream events. These influences may account for the delayed temporal onset of seizures observed in some epileptic syndromes (Zeyden et al., 2008).

In the mammalian brain, the portion of GABA that functions as neurotransmitter is formed by a metabolic pathway commonly referred to as the GABA shunt. As with glutamate synthesis, the most common precursor for GABA formation is glucose. The first step in the GABA shunts the conversion of α-ketoglutarate into glutamate and succinic semialdehyde by the action of GABA-T. GABA is then synthesized primarily from glutamate in a reaction that is catalysed by two glutamic acid decarboxylase enzymes. GABA is packaged into vesicles in the presynaptic terminals by a vesicular GABA transporter proteins. Upon stimulation, GABA is released from nerve terminals by calcium-dependent exocytosis. Once released, GABA freely diffuses across the synaptic cleft to interact with its appropriate receptors on the postsynaptic membrane. GABA signals are terminated by reuptake of the neurotransmitter from the cleft into nerve terminals by the actions of several types of plasma membrane GABA transporters (GATs). The ultimate removal of GABA is achieved by high affinity sodium and chloride dependent uptake GABA into both GABAergic neuron and glial cells (Delorey et al., 1999; Shelp et al., 1999).

GABA-A and GABA-C receptors from membrane channels (ionotropic receptors) and their activation leads to an increased permeability to chloride (Cl⁻) ions. GABA-B receptors belong to the family of G-protein-coupled receptors (metabotropic receptors) activation by directly inhibiting calcium channels or per polarize postsynaptic cells by activating potassium channels (Paredes et al., 1992).

The GABA-A and GABA-C receptor, is a ligand gated ion channel receptor that is an ionotropic receptor. GABA-A are the primary mediator of fast inhibitory synaptic transmission in the central nervous system. GABA receptors are the target for a variety of drugs that enhance GABAergic function for the treatment of diseases such as epilepsy, anxiety, sleep disorders and addiction. GABA-A receptors are pentameric in structure, with the five subunits 2α, 2β and 1γ
arranged like spokes of a wheel around a central Chloride selective pore (Deckers et al., 1997).

Functionally, GABA-A receptors appear to be located postsynaptically. Binding studies have revealed GABA-A receptors with various affinities for GABA, Low, high and intermediate affinity receptor sites, these binding sites are all linked to the opening of the chloride channel. Activation of the GABA-A receptor causes the opening of the chloride ionophore, producing inhibition of neural activity either due to hyperpolarization or to a reduction in membrane resistance.

A characteristic of GABA-A receptor is to be allosterically modulated by other receptors which enhance or reduce GABA effect. These receptors are located near the binding sites of GABA. The convulsant drug, bicuculline, acts as a specific antagonist of GABA on its GABA-A receptor site, while the convulsant drug, picrotoxin, pentylenetetrazole binds and blocks the chloride ions channels linked to GABA-A receptors and directly decrease chloride ion influx. Barbiturates, benzodiazepines and certain steroid like allopregnanolone, progesterone on the other hand, have the opposite effect on the chloride ion channel, which remains open to allow influx of chloride ions into the brain cells (Chebib et al., 2000).

GABA can also inhibit membrane excitability by opening K+ channels and inhibiting calcium channels. These actions are mediated by the GABA-B receptor. GABA-B is a metabrotopic receptor. The structure of the GABA-B receptor is yet unknown, but it seems to be located both pre- and postsynaptically. The activation of GABA-B receptors appears to inhibit the calcium component of the action potential, affecting neurotransmitter release. This inhibition could be explained by a direct coupling of the receptor to the Calcium channels within the membrane through a G protein or could be mediated by a second messenger such as cAMP or protein kinase C. The GABA-B receptors are associated to more than one ionic channel. Electrophysiological studies of hippocampal pyramidal cells have shown that stimulation of GABA-B receptors increases K+ current.
GABA-A receptors are activated by muscimol, whereas GABA-B receptors are activated by baclofen. The GABA-A receptors are blocked by bicuculline, whereas the GABA-B receptor can be blocked by saclofen or phaclofen. Pharmacologically, the GABA-B receptors are insensitive to bicuculline. Glutamate is the principal excitatory neurotransmitter in the mammalian brain. Focal injection of glutamate induces seizures in animals, and over-activation of glutamatergic transmission or abnormal glutamate receptor properties are observed in certain experimental seizure models and human epilepsy syndromes. Inhibition of the neuronal release of glutamate and blocked of its receptors have received considerable attention in the search for novel AEDs (Moldrich et al., 2003; Ure et al., 2006).

2.6.4 Prevention and cure of epilepsy

Theoretically anticonvulsant might act directly on the epileptogenic focus or to prevent the generalization of seizure activity throughout the brain since they may prevent convulsions but do not alter the interictal EEG-record.

The treatment of patients with convulsive seizures can be considered in four parts (Meldrum et al., 2007; Britton et al., 1995; Patsalos et al., 1999 Leach et al., 1995; Tomson et al., 2002; Stefan et al., 2007; Dwivedi et al., 2001).

1) Identification and elimination of factors that might cause or precipitate attacks.
2) Drug therapy to prevent attack.
3) Sustaining mental and physical health aid.
4) Surgical therapy in selected patients with seizures of focal origin.

The basic approach to anticonvulsant therapy is to select an appropriate drug for the specific type of seizure disorder and to progressively increase the dose. Until seizures are controlled or toxic side effects limit further increments.
# Table 2.5 Classification of anticonvulsant drugs

<table>
<thead>
<tr>
<th>No.</th>
<th>Types of seizures</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>Simple partial, complex partial, generalized tonic-clonic seizures</td>
<td>Phenobarbital, primidone</td>
</tr>
<tr>
<td>Hydantoins</td>
<td>Simple partial, complex partial, generalized tonic-clonic seizures</td>
<td>Phenytoin, Mephenytoin</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Simple partial, complex partial, absence seizures.</td>
<td>Diazepam, Clonazepam, Clorazepam, Dipotassium</td>
</tr>
<tr>
<td>Oxazocidinediones</td>
<td>Simple partial, complex partial, absence seizures.</td>
<td>Trimethadione, paramethadione</td>
</tr>
<tr>
<td>Succinimides</td>
<td>Absence of seizure</td>
<td>Ethosuximide, Methosuximide</td>
</tr>
<tr>
<td>Valproic acid and Valproic acid,</td>
<td>Valproic acid, Divalproex sodium</td>
<td>Myoclonic, tonic-clonic</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>Carbamazepine</td>
<td>Simple partial, complex partial, generalized tonic-clonic seizures; Myoclonic, tonic-clonic</td>
</tr>
<tr>
<td>Other anticonvulsants</td>
<td>Gaba-pentin, Lamotrigine, Acetazolamide</td>
<td></td>
</tr>
</tbody>
</table>

Monotherapy: The appropriate antiepileptic drug is given according to the seizure type of the Individual Patient. The treatment usually starts with a low dose of the chosen AED. This dose is gradually increased to reach the anticipated first maintenance dose and then adjusted to clinical response with the aim of achieving seizure control without adverse effects. Drug selection has traditionally been based on the results of clinical trials with different seizure types.
Natural Products Used in the Treatments of Epilepsy

Medicinal plants used in traditional medicine for the treatment of epilepsy have been scientifically shown to possess promising anticonvulsant activities in animal models for screening for anticonvulsant activity. Following natural products plants are reported to have anticonvulsant activity. Albizzia lebbeck (Kasture et al., 2000), Cyperus articulates (Bum et al., 2001), Calotropis gigantean (Argal et al., 2006), Delphinium denudatum (Raza et al., 2006), Guettarda speciosa (Kumar et al., 2010) Glycyrrhiza glabra (Ambawade et al., 2002), Nardostachys jatamansi (Rao et al., 2005), Mimosa pudica (Ngo et al., 2004), Hypericum perforatum (Hosseinzadeh et al., 2005) etc.
2.7 Anxiety

Anxiety disorders are the most common mental illness in the world and became a very important area of research interest in psychopharmacology (Jordan et al., 1996). Anxiety disorder is a blanket term covering several different forms of a type of mental illness of abnormal and pathological fear and anxiety. Anxiety disorders are classified in two groups: continuous symptoms and episodic symptoms (Martinez et al., 2007). Anxiety disorders are often debilitating chronic conditions, which can be present from an early age or begin suddenly after a triggering event. They are prone to flare up at times of high stress and are frequently accompanied by physiological symptoms such as headache, sweating, muscle spasms, palpitations, and hypertension, which in some cases lead to fatigue or even exhaustion (Kessler et al., 2005). In anxiety states, these reactions occur in an anticipatory manner independently of external events. The distinction between a ‘pathological’ and a ‘normal’ state of anxiety is not clear but represents the points at which the symptoms interfere with productive activities.

Although in casual discourse the words anxiety and fear are often used interchangeably, in clinical usage, they have distinct meanings; anxiety is defined as an unpleasant emotional state for which the cause is either not readily identified or perceived to be uncontrollable or unavoidable, whereas fear is an emotional and physiological response to a recognized external threat. Anxiety disorders are often co-morbid with other mental disorders, particularly clinical depression. Anxiety disorders are more likely among those with family history of anxiety disorders, especially certain types (McLaughlin et al., 2005).

2.7.1. Types of anxiety disorder

A) Generalized anxiety disorder

Generalized anxiety disorder (GAD) is a common chronic disorder characterized by long-lasting anxiety that is not focused on any one object or situation. Those suffering from generalized anxiety experience have non-
specific persistent fear and worry and become overly concerned with everyday matters (Morrow et al., 2000).

Anxiety related to GAD often shows up as physical symptoms like insomnia, stomach upset, restlessness, and fatigue. Generalized anxiety disorder is the most common anxiety disorder to affect older adults (Calleo et al., 2008).

B) Panic disorder

In panic disorder, a person suffers from brief attacks of intense terror and apprehension, often marked by trembling, shaking, confusion, dizziness, nausea, difficulty breathing. These panic attacks, defined by the APA as fear or discomfort that abruptly arises and peaks in less than ten minutes, can last for several hours and can be triggered by stress, fear, or even exercise; although the specific cause is not always apparent. In some cases, a heightened awareness (hypervigilance) of body functioning occurs during panic attacks, wherein any perceived physiological change is interpreted as a possible life threatening illness (i.e. extreme hypochondriasis).

C) Phobias

The single largest category of anxiety disorders are that of Phobia, which includes all cases in which fear and anxiety is triggered by a specific stimulus or situation. Sufferers typically anticipate terrifying consequences from encountering the object of their fear, which can be anything from an animal to a location to a bodily fluid. A phobia is an unrealistic or exaggerated fear of a specific object, activity, or situation that in reality presents little to no danger. A specific phobia is an intense fear of a specific object or situation, such as snakes, heights, or flying.

D) Agoraphobia

Agoraphobia is the specific anxiety about being in a place or situation where escape is difficult or embarrassing. Agoraphobia is strongly linked with panic disorder and is often precipitated by the fear of having a panic attack. In addition to the fears themselves, the term agoraphobia is often used to refer to avoidance behaviors that sufferers often develop. For example, following a
panic attack while driving, someone suffering from agoraphobia may develop anxiety over driving and will therefore avoid driving in the future.

E) Social anxiety disorder
Social anxiety disorder (also known as social phobia) describes an intense fear of negative public scrutiny or of public embarrassment or humiliation. Social anxiety often manifests specific physical symptoms, including blushing, sweating, and difficulty speaking. A hypersensitivity to rejection, perhaps related to serotonergic or dopaminergic dysfunction, is present. Social phobia appears to be an interaction between biological and genetic factors and environmental events (Stein et al., 2008).

F) Post-traumatic stress disorder (PTSD)
Post-traumatic stress disorder (PTSD) is an extreme anxiety disorder that can occur in the aftermath of a traumatic or life-threatening event. PTSD is a condition that can develop following a traumatic and/or terrifying event, such as a sexual or physical assault, the unexpected death of a loved one, or a natural disaster. People with PTSD often have lasting and frightening thoughts and memories of the event and tend to be emotionally numb. PTSD is caused by experiencing, witnessing, or being confronted with an event involving serious injury, death, or threat to the physical integrity of an individual, along with a response involving helplessness and/or intense fear or horror. The more severe the trauma and the more intense the acute stress symptoms, the higher the risk for PTSD (Carey et al., 2000).

2.7.2. Causes and contributing factors
Genetic factor: A possible mechanism is malfunction in the parabrachial nucleus, a brain structure that, among other functions, coordinates signals from the amygdala with input concerning balance. The amygdala is involved in the emotion of fear. Especially the basolateral amygdala has been implicated in anxiety generation.

Low levels of GABA: It is an inhibitory neurotransmitter that reduces activity in the central nervous system, contribute to anxiety. A number of anxiolytics
achieve their effect by modulating the GABA receptors (Bhagwagar et al., 2004).

**Alcohol or benzodiazepine dependence:** Approximately half of patients attending mental health services for conditions including anxiety disorders such as panic disorder or social phobia have problems caused by this factor. Though anxiety may pre-exist the dependence, but the dependence acts to sustain the anxiety disorders and often progressively makes them worse (Cohen et al., 1995).

**Exposure to organic solvents:** There is evidence that chronic exposure to organic solvents in the work environment can be associated with anxiety disorders. Painting, varnishing and carpet lying are some of the jobs in which significant exposure to organic solvents may occur (Morrow et al., 2000).

### 2.7.3 Pathophysiology

The brain circuits and regions associated with anxiety disorders are beginning to be understood with the development of functional and structural imaging. The brain amygdala appears key in modulating fear and anxiety. The amygdala and other limbic system structures are connected to prefrontal cortex regions. Hyperresponsiveness of the amygdala may relate to reduced activation thresholds when responding to perceived social threat (Keeton et al., 2009). Prefrontal-limbic activation abnormalities have been shown to reverse with clinical response to psychologic or pharmacologic interventions.

**Common physical symptoms of anxiety**

- Pounding heart
- Sweating
- Stomach upset or dizziness
- Frequent urination or diarrhea
- Shortness of breath
- Dry mouth
- Numbness or tingling in the hands and feet
- Muscle tension
• Tremors and twitches
• Muscle tension
• Headaches
• Fatigue
• Insomnia

2.7.4 Prevention and cure of anxiety (Calleo et al., 2008; Stein et al., 2008)

Benzodiazepines: the most important class, used for treating both anxiety states and insomnia (GABA<sub>A</sub> receptor agonist).

5-HT<sub>1A</sub> receptor agonist: Buspirone (5-HT<sub>1A</sub> receptor agonist)

β-Adrenoceptor antagonists: Propranolol used mainly to reduce physical symptoms of anxiety (tremor, palpitations, etc.)

Barbiturates: Now largely obsolete as anxiolytic/sedative agents (Act partly by enhancing action of GABA)

Miscellaneous other agents: Methaqualone, chloral hydrate
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2.8 COCCULUS HIRSUTUS

2.8.1) TAXONOMIC CLASSIFICATION

Kingdom : Plantae
Subkingdom : Tracheobionata
Division : Magnoliophyta
Subdivision : Spermatophyta
Class : Magnoliopsida
Subclass : Magnolidae
Order : Ranunculales
Family : Menispermaceae
Genus : Cocculus
Species : Cocculus hirsutus

2.8.2) BOTANICAL INFORMATION

Botanical name : Cocculus hirsutus
Family : Menispermaceae (Kirtikar and Basu, 1981)
Synonym : Cocculus villosus, Menispermum hirsutus
Vernacular names (Anonymous, 1950)
Gujarati : Vevati vevdi, vagval
Bengali : Huyer
Hindi : Jamti ki bel
Sanskrit : Garudi
Tamil : Kattukkodi
Telugu : Dusaraitige
Cannad : Dagdi

Distribution: Found in Sudan, Eritrea, Agola, South & Western Africa,
China, Rhodesia, Nyasaland, Pakistan (sind), central Asia, India, (tropical
regions & subtropical regions) (Kirtikar and basu, 1981; Shah, 1978;
Photograph of *Cocculus hirsutus*

Figure 2.8 Photograph of plant - *Cocculus hirsutus*

Botanical description:

Sepals are hairy so it is called *Cocculus hirsutus* (Chopra, 1996).

**Habit:** A climbing scandent shrub

**Leaves:** Leaves are ovate, subdeltoid or 3 lobed, obtuse, mucronate, subcordate at the base. Petioles are very short, dark green, usually subauriculate at the base.

**Flowers:**

Female flowers: 1-3, small, usually clustered in the leaf, axile, pedicellate petals, Thick, flashy, triangular bilobed at the apex. Claw hairy, ovaries two.

Male flowers: Cymose panicles, pedicels, slender, bracts minute, sepals 3, inner are larger, petals thin, emarginated embracing the stamens.


**Flowers & fruits:** February to march

**Roots:** hairy. Dark brown in colour (Shah, 1978; Anonymous, 1950).

**Parts used:** Roots & leaves
2.8.3) AYURVEDIC USES
According to Ayurveda, *C. hirsutus* is known as Patalagarudi in Sanskrit. Root smell is sweetish and pungent, lessen bile and burning sensation, enrich blood. It is used in diseases of urinary system. According to Unani system of medicine, it is antipyretic, tonic, lessens thirsty, good for fractures, and useful in tubercular glands related problems. It is well known herb used as first aid remedy in minor injuries. It alleviates *kapha* and *vata* doshas. It is used as *deepanee, pachanee* and *raktdoshagni*. It possesses light, oily and slimy attributes. It has a special potency as a detoxifier. It is an aphrodisiac and tonic in properties (Anonymous, 2001; 2002).

2.8.4) ETHNOMEDICINAL USES
The roots and leaves of *C. hirsutus* have great medicinal value and are used both, internally as well as externally for medicinal purpose. Root is bitter and used as alterative, laxative, demulcent, tonic, diuretic, antiperiodic in fever, in malaria, joint pains, in treatment of skin diseases constipation and kidney problems (Chopra, 1996; Caius, 1986). Juice of leaves coagulates in water and forms mucilage which is used externally as cooling medicine in eye problems and soothing application in prurigo, eczema, impetigo and dyspepsia. When juice is sweetened with sugar, it is given in acute gonorrhea. Decoctions of the root is mixed with long pepper is used in chronic rheumatism and syphilitic cachexia (Chadhha, 1950; Maasilamani et al., 1981).

The combination of roots of *C. hirsutus* and Caesalpinia crista (latakaranja) seed, matted in water is given orally to alleviate the abdominal pain. Decoctions in combinations with sugar and ginger are used in biliary dyspepsia. Roots rubbed with bonduc nuts in water are given for stomach problems especially in children. Roots act as an aphrodisiac and tonic. The juice of the ripe fruits makes a kind of bluish purple ink. The water soluble fraction of ammonical extract has sedative, hypotensive, bradycardiac, cardiotonic, spasmylytic and slight anticonvulsant actions (Nadkarni, 1976). Due to the presence of phenolic compounds in the
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plant, it is used as anti microbial, preventive infection and enhances healing. Tannins and Flavanoids present in glycosidic combination. Tannins have stringent and healing properties. It is also used in treatment of wounds, burns, and ulcer (Guhabakshi, 1984; Chatterji, 1996).

2.8.5) PHYTOCHEMICAL RIVIEW:
The plant is rich of bis benzyl isoquinoline alkaloids, triterpenoids, essential oil, glycosides, sterols and resins (Chopra, 1982).
Cosculin-N₂ Oxide, trilobine, iso trilobine, coclaurine, & magniflorine which are isolated from stem & roots (Chopra, 1958).
Ahmad et al. isolated Cohirstinine, an alkaloid from the C. hirsutus and structure has been assigned on the basis of the spectral studies (Ahmed et al., 1992).
Raseed et al. isolated Shahinine, an alkaloid from C. hirsutus and structure has been assigned on the basis of the spectral studies (Raseed et al., 1998).
Raseed et al. isolated Hirsutine, an alkaloid from C. hirsutus and structure has been assigned on the basis of the spectral studies (Raseed et al., 1991).
Viquaruddin et al. isolated Cohirsinine, A new alkaloid from C. hirsutus and determination of its structure by 2D NOESY and NOE difference measurements (Viquaruddin et al., 1991).
Viquaruddin et al. isolated trilobine, isotrilobine, syringaresinol and protoquercitol from leaves of C. hirsutus (Viquaruddin et al., 1986).

2.8.6) PHARMACOLOGICAL REVIEW:
Diuretic and Laxative activity:
Ganapaty et al. studied the diuretic, laxative, toxicity activity of the aqueous extract of C. hirsutus aerial parts (100 and 200 mg/kg). It showed significant diuretic activity and laxative effects in rats. The highest dose (400 mg/kg) of the ethanolic extract significantly enhanced urine output. Excretion of cations (Na⁺ and K⁺ ions) and anions (Cl⁻ ions) increased significantly with respect to the control group. The ethanolic extract of the leaves of C. hirsutus (100, 200 and 400mg/kg) and furosemide did not significantly change the concentration of Na⁺, K⁺ and Cl⁻ ions in serum. The ethanolic extract of the leaves of C. hirsutus and
Furosemide increased the excretion of creatinine in urine but with a corresponding decrease in serum. The ethanolic extract of the leaves of *C. hirsutus* (400mg/kg) had significant diuretic effect in rats (Ganapaty et al., 2002).

**Anti diabetic activity:**
Sangameswaran and Jayakar observed significant Anti-diabetic activity of *C. hirsutus* when given as an aerial part extract in normal as well as diabetic rats. The effect, however, was more pronounced in diabetic animals in which administration for fifteen days after streptozotocin induced diabetes, significantly reduced blood glucose levels. After streptozotocin induced diabetes, it was observed that both standard drug (glibenclamide) and methanolic extract of *C. hirsutus* were significantly superior to control in reducing blood sugar on long treatment (15 days). *C. hirsutus* could be of benefit in diabetes mellitus in controlling blood sugar (Sangameswaran et al., 2007)

The aqueous extract of leaves of *C. hirsutus* decreased the serum glucose level and improved glucose tolerance. Total alkaloids reduced the blood sugar level of diabetic rats significantly. Hence, the alkaloids in the roots of *C. hirsutus* have been reported to be responsible for the antihyperglycemic activity. $LD_{50}$ determination (>2000 mg/kg) indicated safety profile of the *C. hirsutus*. The aqueous extract of leaves of *C. hirsutus* has antihyperglycemic activity as it lowers serum glucose level in diabetic mice and significantly increases glucose tolerance. The extract also prevents loss of body weight in diabetic mice (Badole et al., 2007)

**Cardiotonic activity:**
Satyanarayana et al. tested methanol extract of roots of *C. hirsutus* for its cardiotonic activity on diabetic rats and isolated perfused frog heart respectively. The methanol extract exhibited significant cardiotonic activity on normal and hypodynamic frog heart preparation. Activity guided fractionation of methanol extract was carried out. Butanol fraction of methanol extract of roots of *C. hirsutus* was found to have significant cardiotonic activity comparable to that of ouabain (Satyanarayana et al., 2001).
Immunostimulant activity:
The ethanolic and aqueous extract of plant of *C. hirsutus* holds potential as a protective agent against cytotoxic drugs. The extracts when studied on humoral and cell mediated immunity in normal, as well as cyclophosphamide induced immuno suppressed rats. It produced an increase in carbon clearance, humoral antibody (HA) titre, delayed type hypersensitivity (DTH) and WBC count in a dose dependent manner. *C. hirsutus* antagonizes the myelosuppressive effect induced by cyclophosphamide, which produces significant myelosuppression in experimental animal. By the administration of cyclophosphamide Heamoglobin, RBC count, WBC count, Lymphocyte, monocytes, eosinophil count and Platelet count decrease significantly. The present investigation established pharmacological evidence to support the folklore claim that *C. hirsutus* is an immunomodulating drug (Rastogi et al., 2008).

Antimicrobial activity:
Nayak and Singhai performed antimicrobial activity of *C. hirsutus* against *Staphylococcus aureus*, *Pseudomonas aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi* using agar disc diffusion methods using petroleum ether and ethanolic extract crude alkaloid fractions is screened at various concentrations and zone of inhibitions were recorded so bye this result suggest that ethanolic extract has significant antimicrobial activity and used to treat various disease (Nayak et al., 2003). *C. hirsutus* exhibited antibacterial activity by the disc diffusion method. It showed a remarkable antibacterial activity. Pure organic solvents did not show any antibacterial activity. Petroleum ether chloroform, ethyl acetate, acetone, methanol, and aqueous root extract of *C. hirsutus* was tested against *Escherichia coli*, *enterobacter aerogens*, *klebsiella pneumoniae*, *salmonella typhi*, *proteus vulgaris*, and *pseudomonas aeruginosa* (gram negative), *staphylococcus aureus* and *bacillus cereus* (gram positive), pathogenic bacteria. The disc diffusion assay showed that chloroform root extract of *C. hirsutus* inhibits the activity of *pseudomonas aeruginosa* and *bacillus cereus*. Ethyl acetate and acetone extract
exhibit very poor activity associated with *salmonella typhi*, *enterobacter aerogens* and *proteous vulgaris* (Jeyachandran et al., 2008).

**Spermatogenic activity:**
Testosterone levels in the testes were significantly higher in methanolic extract (both 400 and 800 mg/kg) of *C. hirsutus* treated rats after 15th days of treatment compared to the control group. The chronic treatment of the extract for 15 days has increased in the weight of testis, its diameter and seminiferous tubules. There is also a progress in spermatogenesis and increase in *cauda epididymal* sperm count, which may be due to the availability of pituitary FSH during the entire experimental period. The significant increase in the weight of reproductive organs is also indirectly supports the increase availability of androgens. Increased weight and high protein concentration of the testis indicates the enhancement of testicular growth as FSH is essential for protein synthesis in gonads (Sangameswaran et al., 2007)

**Biotechnological activity:**
Tevari et al. investigated the antitumour metabolites production in *C. hirsutus* in cultures and high alkaloids producing cell lines has been established. The pertinent information on the production of antineoplastic agents through tissue culture (Tevari et al., 1992).

**Wound healing activity:**
Panda et al. investigated methanol extracts of the leaves of *Cocculus hirsutus* for wound healing activity. The plant possesses wound healing activity due to the antioxidant or antimicrobial properties of leaves. The methanol extract has highest wound healing activity among the test groups and is comparable to the standard (Panda et al., 2009).

**Anti ulcer activity**
Mallikarjuna rao et al. investigated anti-ulcer activity of leaves ethanolic Extract of *cocculus hirsutus* by using pylorus ligation method. The group of animals treated
with Ranitidine HCl at a dose of 25.57 mg/kg, a significant decrease in the acid volume (14.2 ml) and increase in the gastric pH (3.13) was noted. Group receiving ethanolic extract of *Cocculus hirsutus* at a dose of 400 mg/kg. A significant decrease in the acid volume (12.21 ml) and increase gastric pH 3.13 was observed when compared with the control animals. The observation of ulcer index values the prepared ethanolic leaves extract of *Cocculus hirsutus* having the best anti-ulcer activity compared with standard sample (Rao et al., 2011).


2.9 INTRODUCTION TO PLANT - BARLERIA PRIONITIS LINN

2.9.1) TAXONOMIC CLASSIFICATION:

- **Kingdom**: Plantae
- **Division**: Magnoliophyta
- **Subdivision**: Spermatophyta
- **Class**: Magnoliopsida
- **Order**: Scrophulariales
- **Family**: Acanthaceae
- **Genus**: Barleria (phillipine violet)
- **Species**: Barleria prionitis Linn (porcupine violet)

2.9.2) BOTANICAL INFORMATION

**Botanical name**: Barleria prionitis Linn

**Family**: Acanthaceae (Gaziano et al., 2008).

**Synonym**: vajradanti

**Vernacular names** (Kirtikar and Basu, 1999)
- **Sanskrit**: Vajradanti, Korinta
- **English**: Procupine flower
- **Bengali**: Kantajinti, Peetjhanti
- **Gujarati**: Kantashila, Kantaasheriyio
- **Hindi**: Kala Bans, Katsareya, Piabansa
- **Marathi**: Kalsunda, Kate Koranti, Kholeta, Koranta,
- **Tamil**: Kanagaambaram, Semmulli
- **Telugu**: Mullugorinta, Chettu (Khare et al., 2004; Singh 2006)

**Distribution**: It is found throughout Africa, India, Sri Lanka, Pakistan, Malaysia, Philippines and throughout tropical Asia. It is found in different states of the India include Andhrapradesh, Assam, Bihar, Goa, Delhi, Gujarat, Kerala and Maharashtra (Ata et al., 2007; Shedag 2010).
PHOTOGRAPH OF *BARLERIA PRIONITIS L.*

Figure 2.9 photograph of plant - *Barleria prionitis L.*

**Botanical description** (Dassanayake, 1978, Kamble et al., 2007):

**Habitat:** Barleria prionitis is an erect, prickly shrub, usually single-stemmed, growing to about 1.5 m tall. The stems and branches are stiff and smooth and light brown to light grey in colour. A much branched shrub armed with 2-4, greyish-white, 1-2 cm long sharp, axillary spines (Singh, 2006)

**Leaves:** The leaves are up to 100 mm long and 40 mm wide, and oval-shaped though narrow at both ends (ellipsoid). The base of the leaves is protected by three to five sharp, pale coloured spines, 10–20 mm long. Leaves are sparsely pubescent beneath, scabrid-lineolate above, attenuate, entire, ciliate, bristly acuminate (Fig.2.9).

**Flowers:** The yellow–orange tubular flowers are found bunched tightly together at the top of the plant, but they also occur singly at the base of leaves. The
flowers are 40 mm long and tubular, with several long protruding stalks (stamens). The bracts and calyx are green and oblong-lanceolate, with the outer bract usually foliaceous. The corolla is about 4 centimeters long. Corolla 1.5 cm across, pubescent to glabrous outside, tube 2-2.5 cm long; limb nearly as long as tube, lobes oblong-ovate, obtuse.

**Fruits:** capsule, ovoid, 2 seeded, about 1.5-2 cm long and 0.6-0.8 cm wide.

**Seeds:** The seed capsule is oval-shaped and 13–20 mm long, with a sharp pointed beak. It contains two fairly large, flat seeds, typically 8 mm long by 5 mm wide, covered with matted hairs.

**Roots:** *Barleria prionitis* has a central tap root, with lateral roots branching off in all directions.

### 2.9.3) AYURVEDIC USES

According to Ayurveda, Plant pacifies vitiated vata, pitta, gingivitis, stomatitis, burns, dental caries, inflammations ascites, edema, wounds, nocturnal ejaculation and cracking heal. (Sharma, 2001; Chopra, 1956; Khare 2004, 2007)

### 2.9.4) ETHNOMEDICINAL USES

The leaves and roots are used for a variety of purposes in traditional Indian medicine. In indigenous system of medicine in India, the aerial parts (stem, leaves & flower) are used in catarrhal affections of children, glandular swellings, boils, fever, toothache, inflammation & gastrointestinal disorders; (Nadkarni, 1994; Bhalla et al., 1992).

The whole plant and especially the roots are used as tonic and diuretic. The whole plant is used in urinary and paralytic affections, rheumatism, jaundice, hepatic obstruction, and dropsy. Dried bark is used in cough treatment and the leaves chewed to relieve toothache. The paste of the root is applied to disperse boils and glandular swellings. It exhibits several medicinal properties. The leaves are chewed to relieve toothache. Juice of the leaves is used in ulcer and fever. A mouthwash made from root tissue is used to relieve toothache and treat bleeding gums.
Leaves used to promote healing of wounds, joint pains and toothaches. Extracts used in many herbal skin creams to protect against skin infections. Leaves are also used by some tribal communities for the treatment of piles and to control irritation. Plant extracts known to suppress fungal growth. Mouthwash made from root tissue used for cleaning teeth and relieving tooth ache and bleeding gums. Plant is also used in stiffness of limbs, enlargement of scrotum and sciatica (Ambasta, 1986).

The juice of the leaves, administered in a little honey or with sugar and water, is a favorite medicine in the catarrhal affections of children accompanied with fever and much phlegm; the dose is two tablespoonfuls twice a day. The juice of the leaves, applied to the feet in the rainy season, prevents their cracking or laceration. The juice mixed with honey is applied to bleeding gums. It is also dropped into the ear in otitis Because of its antiseptic properties; the juice of the leaf is used in cataract and fever (Jain 1991; Nadkarni, 1994; Bhalla et al., 1992).

2.9.5) PHARMACOGNOSTICAL AND PHYTOCHEMICAL REVIEW:
Two iridoid glycosides viz. 6-O-trans-p-coumaroyl-8-O-acetylshanzhiside methyl ester and its cis isomer were isolated from B. prionitis. In vitro study showed that these two glycosides possessed potent antiviral activity against respiratory syncytial virus (Chen et al., 1998). Flavone glycoside 5, 6, 4′- trihydroxy-7-0-neohesperidosylflavone was isolated from the fresh flowers of B. prionitis. Two new iridoid compounds barlerin and acetyl barlerin were also isolated from leaf and stem parts of B. prionitis (Rastogi et al., 2001).

2.9.6) PHARMACOLOGICAL REVIEW:
Antibacterial activity:
Ether, ethanol and chloroform extracts of B. prionitis leaves and callus showed antibacterial activity against numbers of gram positive bacterial isolates while no or slight inhibitions were observed by the aqueous extracts. Among these extracts, the ether extract showed strongest antibacterial activity (Shukla et al., 2011).
Antimicrobial activity:
Aneja et al. studied the antimicrobial potential of *B. prionitis* bark against *Bacillus species* was comparable with the standard antibiotic drug (Kamal et al., 2010). *B. prionitis* may be used to treat the bacterial oral infections caused by *Bacillus species*, *Candida albicans* and *Saccharomyces cerevisiae* which has shown greater inhibition zones than the antifungal drugs often used to treat fungal pathogens (Dey et al., 2009).

Antifungal activity:
The acetone, methanol and ethanol extracts of *B. prionitis* bark showed antifungal activity against oral pathogenic fungus *saccharomyces cerevisiae* and two strains of *Candida albicans* (Amoo et al., 2009).

Anthelmintic activity:
The ethanolic and aqueous extracts exhibited significant anthelmintic activity (Chavan et al., 2010). The butanol extract of *B. prionitis* exhibited significant anti-diarrhoeal activity. The butanol fraction also reduced the gastrointestinal motility (Jaiswal et al., 2010). Methanolic extract of *B. prionitis* root showed a significant reduction on spermatogenesis without affecting general body metabolism (Gupta et al., 2000).

Diuretic activity:
Aqueous extract of *B. prionitis* showed significant diuretic and natriuretic effect (Musale et al., 2011). The aqueous extract of leaves of *B. prionitis* showed moderate diuretic activity in rats. The extracts were more potent as diuretic than urea but less potent than potassium acetate (Gupta et al., 2004).

Hepatoprotective activity:
Iridoid glycosides isolated from *B. prionitis* and it was significantly active in glutathione S-transferase (GST) inhibition (Ata et al., 2009). Iridoid enriched fraction from the ethanol-water extract of aerial parts (leaves and stems) of *B. prionitis* was evaluated for hepatoprotective activity in various acute and chronic animal test models.
Antinoiceptive activity:
Singh et al. studied the extracts of flowers of *B. prionitis* for its anti-inflammatory and anti-nociceptive activity. The Extract of *B. prionitis* flower showed significant resistance in pain (Singh et al., 2003). The hydro-methanolic extract of *B. prionitis* showed erythrocyte membrane protection activity in response to the toxic chemicals (Manek et al., 2011).
2.10 INTRODUCTION TO PLANT - BRUCEA AMARISSIMA

2.10.1) TAXONOMIC CLASSIFICATION (Keys 1976, Smith 1985):

Division : Magnoliophyta
Subdivision : Spermatophyta
Class : Magnoliopsida
Subclass : Rosidae
Order : Sapindales
Family : Simaroubaceae
Genus : Brucea
Species : *Brucea amarissima*

2.10.2) BOTANICAL INFORMATION

Botanical name : *Brucea amarissima*
Family : Simaroubaceae
Synonym : Brucea *glabrata* Decne, *Brucea sumatrana* Roxb., *Rhus javanica* L. Biji makassar, Java brucea,
Distribution : India, Sri Lanka and southern China, Taiwan, North Australia. In India is distributed in N. Bengal, Assam, Kerala and in the Andaman Islands. (Anonymous, 1992, 1977, Chang 1987)
Botanical description:
An evergreen shrub (kernels commonly known as Macassar Kernels). The shrubs are erect, chronic, 1 to 2.5 m high with the tender yellow hairs covered on its branches.

**Leaves:** The leaves are compound with 3-15 leaflets; margins serrate. Each serration is formed by the end of a vein bearing a marginal gland. Leaves 20-40 cm; petiolule 4-8 mm; blades ovate or ovate-lanceolate, 5-10(-13) × 2.5-5(-6.5) cm, base broadly cuneate or nearly rounded, usually somewhat oblique, apex acuminate, both surfaces villous, especially along veins and abaxially. Panicles 15-25(-40) cm in males, ca. half as long in females (Keys 1976).

**Flowers:** Brucea amarissima flowers in last march or early april. Young branches, petioles, and inflorescences yellow tomentose. Flowers are small, dark purple, 1.5-2 mm in diameter (Anonymous, 1990; James et al., 2006). Male flowers: pedicel slender, calyx 3 mm; sepals densely puberulent, 0.5-1 × 0.3-0.5 mm; petals sparsely puberulent or nearly glabrous, 1-2 × 0.5-1 mm; filaments subulate.
Female flowers: pedicel; 2.5 mm; sepals and petals same as in males; stamens rudimentary.
Seeds: yellowish white, ovoid, thinly membranous, with copious oil, terribly bitter.
Fruits: 1-4 druplets, purple to black in colour when ripe. The fruit is oval, about 8 mm long (Anonymous, 1989; 1990; Keys et al., 1976).
Flowering: Jun-July
Fruiting: August-October

2.10.3) ETHNOMEDICINAL USES
The roots and fruits are used against diarrhoea, dysentery and fevers. The crushed leaves are used medicinally against ring worms, scurf, boils, centipede bites, internal pains, and tumour-mainly skin cancer (Kitagawa, 1994). It is used to treat dysentery, malaria and cancer and applied to burns, bleeding due to traumatic injuries, haemorrhoids and ulcers in the mouth (Yeung 1985).

Java brucea seed has bitter, cold, and slightly toxic properties. The seeds are associated with the Large Intestine and Liver meridians. It has been used for centuries to treat dysentery and malaria. Externally, Seed can be made into an ointment to treat foot problems such as corns, and also skin conditions such as warts. There is also some evidence that brucea, in combination with longan, may be effective in treating some types of cancerous tumors (Ong et al., 2004; Sudarsono, 2002).

It is mainly used to treat dysentery, malaria, and wart (excrescence), and to eliminate the whipworm, roundworm, tapeworm, and trichomonad, and curb influenza virus, with an effect on anti-malaria and anti-tumor, as one of the good medicine materials having been used since time immemorial (Lin et al., 1990)

2.10.4) PHYTOCHEMICAL REVIEW:
Kim et al. isolated Quassinoid glucosides, javanicosides I, J, K and L from the seeds of *B. amarissima* (Lour.) (Simaroubaceae), along with two known quassinoids, i.e. bruceins D and E, and seven known quassinoid glucosides, yadanziosides B, C, E, I and K, bruceoside B and yadanzigan. Their structures
were elucidated by analysis of the spectral data and chemical evidence (Kim et al., 2004).

Sato et al. isolated brusatol, another quassinoid from the seeds of *B. javanica*, was also reported to be effective in the treatment of dysentery (Sato et al., 1980).

Thakorn et al. derived antibacterial peptide from the fruit of *B. amarissima* Desv. Pepsin hydrolysis of the fruit made up many peptide fragments but only a peptide of mass about 1350 which had the potent inhibitory effect to the growth of *S. pyogenes* (Thakorn et al., 2000).

2.10.5) PHARMACOLOGICAL REVIEW:

**Amoebicidal activity**

Keene et al studied that a crude butanol extract of *B. javanica* was highly active against *Entamoeba histolytica*. This amoebicidal activity was associated with two polar compounds isolated from the extract, bruceantin and brucein C, which are quassinoid constituents (Keene et al., 1986).

Wright et al studied that *Brucea* quassinoids were active against *E. histolytica* and other protozoa *in vitro*. The quassinoids were potent inhibitors of protein synthesis both in mammalian cells and in malaria parasites and it has been suggested that this effect accounts for their amoebicidal activity (Wright et al., 1993, 1988).

**Antibacterial activity**

Wasuwat et al reported that the Extracts from the kernels of *B. javanica* possess antibacterial activity against *Shigella shiga*, *S. flexneri*, *S. boydii*, *Salmonella lexington*, *Salmonella derby*, *Salmonella typhi* type II, *Vibrio cholerae inaba* and *Vibrio cholerae ogawa* (Wasuwat et al., 1971).

**Antiplasmodial activity**

Ayudhaya et al performed *in vitro* activity of bruceantin, a quassinoid constituent of the drug which exhibited significant antiplasmodial activity against *Plasmodium falciparum* (o’ Neill et al., 1986; Ayudhya et al., 1987).
Antimalarial activity

Pavanand performed *vitro* activity of extracts against chloroquine-resistant *P. falciparum* and *in vivo* against *P. berghei* (mice). Nine quassinoid constituents of the drug had *in vitro* IC$_{50}$ values of 0.046–0.0008 mg/ml against chloroquine-resistant *P. falciparum* strain K. Bruceolide, another quassinoid constituent of *B. javanica*, were also effective *in vivo* (mice) against *P. berghei* and were reported to be more effective than chloroquine (o' Neill *et al.*, 1987; Pavanand *et al.*, 2001; Ngo *et al.*, 1986).

Darwish et al isolated Quassnoids from *B. javanica* for cytotoxic activity *in vitro* (Darwish *et al.*, 1979; Ohnishi *et al.*, 1995).