Chapter 1
INTRODUCTION

Natural world have excellent of compounds, and wide variety of plants with therapeutic properties for thousands of years. For medicinal purposes, it is unsurprising that, about 70,000 plants genus from tiny herbs to huge trees have been used from beginning of time. The employ of medicinal plants as a base to heal the diseases can be traced back to more than five millennia. Paper qualifications of the early civilizations in certain countries (Near East, India and China) are a talent as mature as humanity without any doubt. Still, medicinal herbs are the exclusive foundation of drugs, for the mass of the population and help its liberation from sickness. The entire useful crude drugs have been thoroughly studied botanically and histologically. Thus, botanically oriented sciences of Pharmacognosy become stagnant. Current investigation on herbal is paying attention to the separation of phytococonstituents from the crude drugs. The herbal medicine contains chemical constituents whose special effects are verified pharmacologically.

The herbal drugs are vital resource of medicines, used in recent health care organizations. The world wide approval of plant-derived drugs has given an impulsion to remarkable development of medicinal and aromatic crops. In India, more than 10,000 spices of therapeutic herbs are being used steadily in formulation of original medicines and for the current drug delivery systems. The genuinity of herbal drugs and their accessibility for marketable investigation are two significant necessities for mass herbal drug production. A variety of significant medicinal plants has been fundamentally examined from all various angles of analysis. These drugs have been prescribed by Vaidyas and Hakims. The chemical composition of these drugs has been strong-minded and the genuine intrinsic worth of these drugs have been proved by the action of the active principles, worked out by mice experimentation.

Plants and normal crops played fundamental task in the handling of different illnesses as unpolluted compounds. They suggest priceless supply of compounds with a broad range of chemical structures, biological activities and offer important prototypes for the
expansion of narrative drugs. There is an enormous choice of compounds that can be extracted from the plants, which permits the demonstration of their physiological activity. Our body is, all the time bare to toxic organic compounds from both intentional and unintentional sources. To bound, both systematic effects, length of therapeutic action, fast and regimented removal of these substances is crucial in the resistance scheme of our body.

Many small changes and addition have been made throughout the context so as to include the results from recent researches. Several new illustrations have been added to help clarify the descriptions. Crude drugs of vegetable, animal and mineral origin form the subject matter with which pharmacognosy is concerned. Example :: Senna leaves and thyroid glands: a few such as light kaolin and chalk, are minerals others again are substances derived from plants or animals by more or less elaborate processes of extraction eg: catechu, aloes, opium, resins. The constitution of molecular structure and properties of these chemical entities fall within the province of chemistry, it is only their occurrence as constitutes of crude drugs and their general properties as members of classes of constituents that are included in pharmacognosy.

Thus only the anatomical or histological studies have received the sole attention of the pharmacognosists. By this method, based mostly upon the study of the tissues, the identity and general quality of drugs and foods are ascertained. The results thus obtained, when taken in conjunction with those of chemical analysis, have been of great value in determining the purity of the products examined. Over three centuries the world population relies mainly on plants one or other was used for medicinal purpose.

Herbs are staging a comeback and herbal renaissances are happening all over the period. The herbal yield now provides security that is regarded as non-dangerous to person and surroundings. Though, the sightless reliance on production is in excess the populace is recurring to the nature with expectation of sanctuary and defense. It has been predictable that in urbanized countries such as USA plant drugs comprise 30% of the whole drugs, even as in quick budding nations is a great deal as 82%. While, plants have been priced for their therapeutic and perfumed properties for centuries. The artificial crops of the new period surpassed their importance, for a while. In our country herbal origin drugs have been used in the traditional systems of medicines such as Unani, Sidha and Ayurveda.
The rapid development of different aspects of crude drugs in recent years has necessitated a systematic approach in their study in modern pharmacognosy. The crude drugs supplied to pharmaceutical, phytochemical and perfumery industries are frequently adulterated by foreign organic matters, resembling the standard drugs or substituted by inferior quality of herbs. In pharmacognosy, it is concerned with the cell contents which can be identified in plant drugs microscopically, chemo-microscopically and or by physical tests.

At no time in the narration, progress has been so rapid and so meaningful as that achieved in the last decades, in our understanding of drugs of natural origin. The substantial scientific work that has been accomplished in recent years in the field of pharmaceutically significant natural products has revolutionized the entire concept of Pharmacognosy. The ultimate biomedical objective of pharmacognosy is to contribute to the rational relationship between chemical moieties of naturally occurring drugs and biological and therapeutic effects they generate.

Every system of the world, including science, has developed through critical comments, discussion and suggestions. When the criticisms are abnormal and beyond limits then there is a challenge. The traditional drugs are discussed to provide link between current findings. The term „materia medica” is used to refer to all substances used in medicine such as; pure chemical compounds, herbal drugs, mineral substances, and biological preparation like vaccines and sera. At present pharmacognosy involves the study of crude drugs and their natural derivatives. The plant medicines are significant foundation of drug used in current physical condition. The worldwide receipt of usefulness of plant related drugs has known to create a momentum for profitable farming of therapeutic and fragrant crops. The genuinity of herbal drugs and availability for commercial exploration are two important requisites for sound herbal drug industry. Either single or different parts of the same plant can be used as source of drug and hence it becomes necessary to know various parts of a plant scientifically.

Nowadays, pharmacognosy is extremely particular science that represents one of the major disciplines of pharmaceutic education. During the past few years, as consequence of the strong anxiety with all relation of environmental science, has rehabilitated the interest in known natural foods and drugs. Consequently a vast literature on natural drugs written by laymen and indented to inform has come to existence. Due to the attention, it
engenders many of the researchers at the moment. Study of herbals is a valued regulation that has no foil in the other area.

A number of the drugs used by the ancients are still employed, in much the same manner by today’s medical practitioners. However, an intuitive curiosity is inherent in the average person who reads or hears about pharmacognosy. Pharmacognosy is concerned with the study of crude drugs of vegetable, minerals and animal origins. The term material medica is used to refer to all substances used in medicine such as pure chemical compounds, plant drugs, minerals substances and biological preparations like vaccines and sera. This study involved a comprehensive study of individual drugs and elucidation of general principles. At present pharmacognosy involves the study of crude drugs and their natural derivatives. Thus, digitalis is isolated glycoside; digoxin, datura and its isolated alkaloid, atropine opium and its purified compound morphine, all are treated as the subject of pharmacognosy. For the study of crude drug, the following points must be taken for consideration.

**Biological source:** the biological source of a drug is mentioned in Latin language which also includes the family to which it belongs. After the Latin name, the name of botanists responsible for the classification is mentioned in abbreviated form. The plant family to which the drug belongs determines certain of its characters like;

**Haunt:** The principal areas of collection and routes of transport are considered under this subject.

**Plant territory:** The all-purpose arrangement of the plant and morphology of crude drugs are intentional.

**Cultivation, collection and preparation for market:** These factors require particular attention when they affect the appearance or quality of the product.

**Morphology and organoleptic characters:** Knowledge of the fine details of macroscopical structure is important in the examination of pulverized drugs.

**Microscopical study:** Microscopical characters such as cell array, starches, epidermal trichomes, calcium oxalate crystals and fibers are studied under this topic.
Commercial varieties, substitutes and adulteration: With knowledge of the indicative characters of executive drugs, a decisive assessment may be made of profitable samples to resolve their eminence, substances known to be latent substitutes.

Active constituents: The pharmacological principles the percentages of the further persuasive components of affect the mode of research the identity and the class of such compounds are considered.

Evaluation of herbs: The clarity and quality of drugs are determined.

Uses: A variety of medicinal uses and toxic effects are studied.

In present global scenario, natural medicines are gaining prominence, because they are economical, easily available and relatively free from side effects. The greater than before universal requirement for plant preparations is reflective of the positive impact of considerable efforts aimed at reviving science of Phytopharmacognosy. Modern Pharmacognosy, deals the cultivation technology, quality control of herbal drugs, phytochemistry, phytopharmcy and therapeutic utility of crude drugs. The emphasis is given on current trends in herbal drugs, ayurvedic pharmacy, marine pharmacognosy, nutraceuticals and medicinal plant biotechnology and endangered species of medicinal plants.

1.2 Modern Pharmacognosy

Modern pharmacognosy has been developed rapidly due to the improvement made in the technology of separation processes, which incorporate the improvement of chromatographic techniques such as column, paper; thin layer, gas-liquid, HPTLC, HPLC and droplet counter current procedures. The most imperative factor has been the improvement of new spectroscopic techniques which are used to recognize structures of the secluded compounds. Simultaneously advancement in the fields of chemistry, biochemistry, biosynthesis and pharmacology has developed Pharmacognosy (Mohammed 1998). Although more than 100 plants are used in modern medicine in various parts of the world, the list of most important ones along with their pharmacological properties is given in Table 1.
Table 1. Important Active Principles of Herbs Used in Medicine

<table>
<thead>
<tr>
<th>Herbs</th>
<th>Active Principles</th>
<th>Therapeutic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berberis sp</td>
<td>Berberine</td>
<td>Anti-diarrhoeal</td>
</tr>
<tr>
<td>C.roseus</td>
<td>Vinblastine, vinchristine</td>
<td>Anticancer agent</td>
</tr>
<tr>
<td>Cephaelis acuminate</td>
<td>Emetine</td>
<td>Anti-amoebic</td>
</tr>
<tr>
<td>Cinchona sp.</td>
<td>Cinchonine</td>
<td>Antimalarial</td>
</tr>
<tr>
<td>Claviceps purpurea</td>
<td>Ergotamine and ergotoxin</td>
<td>Oxytocic</td>
</tr>
<tr>
<td>Coffea Arabica</td>
<td>Theophylline</td>
<td>CNS stimulant, diuretic</td>
</tr>
<tr>
<td>Colchicum</td>
<td>Colchicine</td>
<td>For gout</td>
</tr>
<tr>
<td>Digitalis lanata</td>
<td>Lanatosides and digitoxin</td>
<td>Used as cardiotonic</td>
</tr>
<tr>
<td>Discorea sp.</td>
<td>Steriodal hormones</td>
<td>Anti inflammatory and antiarthritic agent</td>
</tr>
<tr>
<td>Agave sp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythroxylum</td>
<td>Cocaine</td>
<td>Anaesthetic</td>
</tr>
<tr>
<td>Glycyrrhiza glabra</td>
<td>Glycyrrhetic acid</td>
<td>Anti-inflammatory agent</td>
</tr>
<tr>
<td>Theobroma</td>
<td>Theobromine</td>
<td>CNS stimulant</td>
</tr>
</tbody>
</table>

1.2.1 Plant Constituents

Modern pharmacognosy deals with a varitery of plant constituents. The medicinal value of crude drug depends on the presence of one or more chemical constituents of physiological importance. They may be glycosides, alkaloids, organized resins, enzymes etc. A vegetable drug is composed of a number of tissues such as cells, fibres, vessels and other structures. The cell wall may consist of cellulose, lignins, tannins or cork cells. The cells of aromatic drugs like coriander, cinnamon, clove and fennel contain volatile oils occurring in specialized cells or glands. The glycosides and alkaloids may transpire in solution in the cell sap and deposit in the cells later on. The unorganized drugs possess no
cellular structure but consist of extracts, exudation, secretions, latex and other products of the plants. The total contents of the cell are not used as physiological importance. The constituents of drugs of medicinal value generally belong to one of the following group: glycosides, anthraquinone derivatives, alkaloids, tannins and other phenols proteins, carbohydrates, gums, resins, fat, fixed oils, volatile oils and waxes.

1.2.1.1 Carbohydrates

Carbohydrates are the primary products of photosynthesis and from them the plant synthesizes various chemical constituents by subsequent organic reactions. The carbohydrate includes simple sugars and polysaccharides. These plant products contain carbon, hydrogen, and oxygen. Carbohydrates which are usually scattered in herbs, supply storage and transportation of energy and structure blocks to the cell wall (Mohammed 1998).

Examples: Honey, starch, acacia gum, tragacanth, pectin etc.

1.2.1.2 Glycosides

Glycosides are compounds which upon hydrolysis give rise to one or more sugars and a compound which is not a sugar moiety. In glycosides the hydroxyl of a sugar is condensed with the hydroxyl of the non-sugar component. In plants only beta forms of glycosides are formed, even if the alpha linkage is detected in nature, in some carbohydrates such as sucrose, glycogen and starch. Most of the glycosides are colorless, crystalline compounds. Anthracene glycosides are red or orange coloured compounds and flavones glycosides are yellowish in colour. They are soluble in water and alcohol, but insoluble in other organic solvents like petroleum ether and carbon tetrachloride Glycosides are optically levorotatory. Glycosides are used for the treatment of various illnesses.

Examples: Rhubarb, Senna, Aloes, Squill, Strophanthus etc,

1.2.1.3 Alkaloids

The term alkaloid is applied to naturally occurring basic compounds and is difficult to define. The term is derived from "vegetable alkali" (alk = alkali; oid = like). They may be defined as organic nitrogenous substances of plant origin exhibiting well-defined physiological actions A true alkaloid has a nitrogen atom as a part of heterocyclic system; it has a complex molecular structure; it manifests significant pharmacological activity and it is restricted to the plant kingdom. The names of alkaloids have been derived from the plants
yielding them (atropine, tylophorine, cocaine, nicotine); from physiologic activity (emetine, morphine) and from the discoverer (pelletierine, alhiirsexine). As per chemical rules the names of all alkaloids should end in “ine”). Alkaloids exhibit a variety of physical and chemical properties. They are generally colourless compounds but few are coloured substances, e.g., berberine (yellow), betaine (red), tylophorine (dull yellow), and conessine (pale yellow). They are generally bitter in taste and optically active.

Alkaloids are capable of exhibiting extensive and well-marked pharmacological activities like analgesic (cocaine, morphine, codeine), antiamoebic and emetic (emetin), anticholinergic (atropine, hyoscyamine, scopolamine), antihypertensive (reserpine, deserpine), antimalarial (quinine.cinchonine), antitumor (vinblastine, vincristine), antitussive (codeine, noscapine), cardiac depressant (quinidine), central nervous stimulant (caffeine, strychnline, brucine), diuretic (theobromine, theophylline), oxytocic (ergometrine, ergotamine) ophthalmic and cholinergic (physostigmine, pilocarpine), skeletal muscle relaxant (tubocurarine) and smooth muscle relaxant (papaverine, theophylline).

1.2.1.4 Resins

Resins are solid or semisolid plant exudates formed in schizogenous or schizolysigenous ducts or cavities. They are complex mixtures of compounds like resin alcohols (resinols), resin acids, resinetannols (resinphenols), esters and resenes. Some resins (e.g. Benzin and Balsam of Tolu) are formed when the plant is injured. These resins are called as pathological resins. The resins commonly used in pharmacy are derived from natural sources, and almost are plant products. Shellac, an insect secretion, being an important exception. Characters: Purified resins are amorphous, brittle, translucent, hard solids. On heating they are softened and then melted. They are practically insoluble in water but dissolve in organic solvents like alcohol, ether and chloroform. Varnish-like film is formed on evaporation of the solvent. They produce smoky flame on burning.

Examples are Balsm of Peru, Balsm of Tolu, Colophon and Myrrh.

1.2.1.5 Essential oil or Volatile oils

Volatile compounds are flavouring compound which evaporates on exposure at ordinary temperature. They are present in various plant parts such as flower petals (saffron), fruits (fennel and coriander), bark (cinnamon) etc. They are secreted in particular
secretory cells like glandular hairs, modified parenchyma cells, vittae or lysigenous or schizogenous cavities. Chemically these are a mixture of monoterpene and sesquiterpenes. They may be simple hydrocarbons, alcohols, ketones, aldehyde, phenols, ethers, esters, acids, oxides and aliphatic or aromatic compounds. Essential oils are colorless liquids or, crystalline or amorphous solids. Like fixed oils they do not form permanent strains and cannot be saponified by alkalies. They are slightly soluble in water, but highly soluble in ether, alcohol and other organic solvents. Phenolic volatile oils are present in drugs like Thyme, clove and pine tar. They are having antibacterial, antiseptic and antifungal activity. They are perfumery, flavouring compounds and have been used in perfumery from ancient times.

Examples: Coriander, clove, fennel, camphor, etc.

1.2.1.6 Tannins

Tannins are complex organic, non-nitrogenous derivative compounds of poly-hydroxyl benzoic acids which are widely distributed in the vegetable kingdom. They are the active compounds of material like oak tree, which are used in the tanning of skins. They are present in the aerial parts, like leaves, twigs, fruits, stem or barks etc. They are probably protective to the plant during the growth and are destroyed or deposited as end products of metabolism in some dead tissues of the mature plant i.e.: outer cork, heartwood, galls etc. Some phenolic compounds such as gallic acid, catechins and cholrogenic acid often occur with tannins and are called as pseudo-tannins (Mohammed 1998).

Tannins are astringent in taste, soluble in water; yield purple, violet or black colour precipitated with iron compounds. Tannins are precipitated and combined with proteins. The protein tannin complex is resistant to proteolytic enzymes. This property is known as astringent action and due to this; tannin-containing drugs are used in medicine as astringent. During healing process of burns, the protein of the exposed tissues is precipitated producing a mildly antiseptic protective layer under which the new tissues are regenerated. Aqueous solution of tannins is used as anti-inflammatory agent, treatment of leucorrhoea, gonorrhoea, burns, piles, and antidote in the treatment of alkaloid poisoning. Tannins from deep coloured complex with iron salts and are worn to manufacture of inks.

Examples of tanning containing compounds are nutgall, black catechu and pale catechu, krameria, Hamamelis.

Department of Pharmacy, JJT University, Rajasthan
1.2.1.7 Fats, Fixed Oils and Waxes – Lipids

The term lipid is used for fixed oils, fats and waxes. Fixed oils are liquid at normal temperature; while fat are solids or semi solids normal or room temperature. Chemically they are esters of glycerol with long chain fatty acids. These are termed as glycerides. These components are obtained from plant or animal origin. There are no differences between fats and oils. The fatty acids may be saturated or unsaturated, but generally they contain unbranched carbon chain and have been even number of carbon atoms.

Most of the saturated glycerides are called fat at ordinary temperature, but most unsaturated glycerides are oily liquids. Therefore, the vegetable oil contains large propositions of unsaturated glycerides than the solid animal fats. The identity, purity and quality of fatty substances are determined by finding out their acid value and saponification value (Mohammed 1998). Fatty acids are used to treat skin lesions, wounds, burns, sunburns, dandruff and eczema. It is also used as laxative, emollient in the preparation of suppositories, liniments and ointments as a source of Vitamin A, Vitamin D and Vitamin E as antifungal agent and in the manufacture of soaps, glycerine, paints, lubricants and varnishes. Chaulmoogra oil is used for cure the leprosy diseases.

Examples of fixed oils are castor oil, shark liver oil, seame oil, olive oil, and theobroma oil etc.

1.3 Variability in Drug Activity

During the development of plants, there is a considerable variation in size, shape, color and other characters within a given population. There is also a difference in the content of the active constituents in the fresh drug. The content of the active constituents and the ratio between different constituents are not static, but dynamic, vary in the living organisms according to the interaction of factors inside and outside of the organisms. Due to complexity of life process and as change in one factor affects the influence of another factor, it is generally difficult ascertain to exact affect of a given factor.

As a rule, there is a greater variation in the content of medicinally active components, which are secondary metabolites, than in the contents of normal metabolites and storage products. For example, fat content of bitter almond varies from 40 to 63% but the amount of amyglalin differs from 0 to 8.5%. The variation of therapeutic components in some
Drugs are as: atropine in belladonna leaf (0.3-1.7 %), alkaloids in cinchona (4-14 %),
glycosides in digitalis leaf (5.5-21 units), alkaloids in ergot (0-0.2 %), glycyrrhizin in
liquorice (3-12 %), morphine in opium (3-12 %) and menthol ester in peppermint oil (2-11 %).

The quality of crude drug depends on the amount of the active compounds
present in it. Variation in the morphology or in concentration of active constituents may be
due to several factors, including genetic factors; differences in the environmental conditions
or due to methods used in the collection, preparation and storage of the crude drug.

1.3.1 Effects of Endogenous or Genetic Factors

Members of a given species are rarely genetically homogenous. When the
genetic difference is great, which resides in the genes, the morphology and biochemical
diversity for each species are different. They can bring about differences in the amount or the
type of chemical constituents produced. Whenever such biochemical variation occurs, each
particular type is known as a „physiological variety”. Thus, there is no difference between
bitter and sweet almond trees, but the seeds of the former contain a bitter glycoside
(amygdalin). (Duboisia myoporides of northern Australia produces mainly scopolamine, while
this plant grown southern Australia yields chiefly hyosciamine). Eucalyptus dives of
Australia yields an essential oil that varies greatly in odour and chemical contents from tree to
tree. On the basis of the chemical composition of the oil, four physiological varieties of the
tree have been distinguished.

The seeds of strophanthus sarmentosus are biochemically polymorphic. The
variety from the Belgian Congo produces sarverogenin; variety from French sudan yields
sarmentogenin; and where as the variety from French Guiana gives very small amount of
either compound. Morphological differences are insignificant. Similar variation is observed
in varities of camphor trees; in red and white squills; in rauwolfia etc, some types of Rheum
Palmatum are high in rhein, others are low in this compound. There is a little variation in the
content of chrysophenol. Among the three forms, of diphtheritic organisms known as gravis,
media and mitis. Mitis causes much less serious infections when compared to others.
1.3.1.1 Selection

There is a variation in the intensity of expression of any given characteristics in any given population of plants. The plants may be genetically heterogeneous to some extent. Genetrical differences exist normally from one plant to other. If, the plants having most desirable characters which are chosen, for inter-breeding. The derived second population may have a tendency towards improvements with respect to that particular quality. Continued selection and breeding of the most desirable plant will greatly improve the particular quality chosen. If the plants are of a „pure breed” and all variation is due to environmental selection then breeding will have no effect.

Selective breeding of medicinal plants has resulted in plant with increased constancy of quality, increased growth, resistance to disease, winter hardiness, and other desirable characteristics. It is a tedious and time-consuming task. Selection work on Cinchona ledgeriana with about 5% alkaloids has furnished types which yields bark, with up to 15% alkaloids. Selection programmes with mentha arvensis have developed drought-resistant and the rust-resistant types yielding high amount of menthol. The rotenone content of Derris (insecticides) has been raised from 3%-13% in some clones by selective breeding.

The average yield of essential oil in several plants has been improved by selective breeding. Selection work is vital in the fermentation industry where high yielding strains suitable for certain economical medias are developed. In nature, some strains of a given microbe are active in producing antibiotics, (e.g. the strain of Bacillus subtilis from the throat of Mary Tracy is used industrially). Careful selection of active strains is significant to produce toxins, vaccines, and other pharmaceutical products.

1.3.1.2 Mutation

Exposure to ionizing radiation (x-ray, γ-rays, radioactive isotopes) or non-ionizing radiation (ultraviolet) or some mutagenic chemical agents, may change the nature of a gene artificially. These changes, (mutation) generally may cause the gene to lose its function entirely or in part; or it may cause the gene to do a different job. Mutation may also arise spontaneously in nature. Nothing is known about such changes. The mutant gene is passed from the parent to the progeny in its changed form. Genes control the biological and
morphological characters. Genes determine the presence of enzymes which catalyze the formation of vital biochemical metabolites.

The original strain of *Penicillium chrysogenum*, used in the production of penicillin yielded about 100 units of penicillin per ml of the culture medium. By single-spore isolation, strains which yielded up to 250 units per ml of cultured medium. X-ray treatment of this strain yielded mutants which could produce 500 units per ml, and UV (Ultra Violet) mutants of the latter gave strain which produce about 1,000 units per ml. Similar improvements have been obtained with other antibiotic producing organisms.

Mutation and selectin helps to and are resistance to chemotherapeutic agents by pathogenic microbes. When a microbe is cultured in a medium containing an antibiotic to which it is sensitive, majority of the organisms will be eliminated by the antibiotic, but a few organisms will survive which are mutant resistant to the antibiotic. The resistant organisms are free to multiply and grow here by giving rise to a new population, which is resistant to the given antibiotic.

Mutation is a random process occurring at all times. In an industry, the strain of organisms used should be entirely pure and uniform, since any change in the strain of the organism used in the fermentation process may cause great economic loss and danger to human lives. Therefore, the stock cultures are maintained under very stringent conditions, and constants checks to ensure their uniformity.

Genetic changes in plant involves multiplication of entire chromosome set to give 3n, 4n, 6n, etc. In body cells polyploidy (addition of 1 or a few chromosomes, extrachromosomal type), gross structural changes and submicroscopic changes or point mutations include alteration in DNA chromosomal material. Such Mutations constantly occur in nature at a slow rate. Many mutations are of recessive type and do not become apparent until, the F₂ generation of the self –pollinated plant.

**1.3.1.3 Polyploidy**

Each living cell contains in its nucleus 2 sets of chromosomes. Since the chromosomes in the nucleus are present in duplicate, the normal cell is referred to as a diploid cell. If the chromosomes reduplicate with in the nucleus, 4 sets of chromosomes are formed without subsequent division of the cell. In this way the condition arises where in the nucleus
contains more than its normal compliment of chromosomes. This condition is called as “polyploidy”. Through various mechanisms, a condition may arise in which the cell contains 3 sets of chromosomes (triploidy); or 4 sets (tetraploidy), etc. Polyploidy may develop in a plant through natural means, or by treating the cells (especially the seed) with heat with colchicines or other specific compound. Various changes take place in the chemical composition of the individual due to the changes in the chromosome component of the nucleus.

The most prominent changes brought about are in the size of the plant and its organs, along with some physiological changes. In the presence of colchicine, chromosomes in a cell under going mitosis, divide without the formation of mitotic spindle fibers. Therefore, sister cells are not formed. A 72 hour treatment of the growing root tips of onion with colchicine solution produces 256 chromosomes. The “c-mitotic” activity of colchicine may arise from its interaction with the disulphide bonds of the spindle protein and by inhibition of the conversion of globular proteins to fibrous proteins on discontinuation of treatment, the spindle figure again forms in the normal way. Colchicine is 100 times more active than its isomer isocolchicine while colchicines are almost inactive.

Plant material is treated with colchicines in various methods. Seeds are soaked in an aqueous solution of colchicines (0.2-2.0%) for 1-4 days before planting. Seedlings are imported on to filter paper soaked in the solution for the protection of growing plants. In other methods, soil around the roots of young seedlings can be moistened with the colchicines solution. Young buds and shoots are also treated by immersion lanolin pastes and agar gels are used in tissue culture techniques.

Newly formed polyploids are stabilized themselves for a number of generations. Such types of treatments do not give a uniform plant concerning chromosome number. Typical effects of polyploidy include larger flowers, pollen grains and stomata. With lobelia, the tetraploid plants are smaller than the diploid ones. With tetraploids caraway plants, the total volatile oil content is increased by 100%. In opium, the concentration of morphine increases up to 100%.

In some species polyploidy does not affect the relative proportion of a compound. However, solanaceous herbs produce excess quantity of tropane alkaloids in the

*Department of Pharmacy, J JT University, Rajasthan*
4n state and reduced amount as haploids. The proportion of carvone in oil of caraway obtained from 4n plants is also different. *Digitalis lanata* in 4n state contains a relatively high proportion of lanatosides A and B in comparison to 2n form. There is also a difference in the sequiterpen lactose of *Ambrosia dumora* in the diploid and polyploidy state.

Some medicinal plants have shown an increase in the content of active constituents on induction of polyploidy. (Colchicines-induced tetraploidy of datura stramonium produced 2 times more alkaloid than the normal diploids). An increase in alkaloid content has been observed in polyploids of lobelia and nicotiana species. Tetraploids of a cinchona species contain 1.1% of alkaloid, more than twice the amount contained in the diploid plants.

### 1.3.1.4 Hybridization

The mating of inherently different individuals to produce hybrid progeny is called „hybridization“. Some desirable biochemical or morphological characteristics may be developed in to the progeny by this process. Genes are introduced by hybridization to decrease resistance to decrease, increase stature, for excess production of starch and vitamins, different colour of the flowers, etc. Hybrids of cinchona yield more amount of quinine. A hybrid developed by crossing *C.succirubra* with *Cinchona ledgeriana* yields a bark which contains 11.2% of alkaloid. The parent species produced 3.4 % and 5.1% of the alkaloid respectively.

Each planting must be made with new hybrid seed by crossing in original parent species. The seeds will produce progeny which are not uniform, some reverting to the parental types, and other being of intermediate types. When plants of peppermint are allowed to mate at random, the resulting seeds give rise to plants of varying composition. A gradual change occurs in-favour of the oil from spearmint hybrid yielding oils of different composition. For maintaining genetic purity of peppermint and spearmint hybrids, the plants must be propagated by planting stolons.

### 1.3.2 Influences of Ecological and Exogenous Factors

Ecological factors play a vital role in the activity of drugs. When the drug is with very good quality features, drug industry people will pay a good price for the herbs. World wide varieties plant spices are available and as these herbs are scattered it is very
difficulty to process and collect. In this stage there is huge demand for some herbs and it has become necessity to process these in a huge scale more than ever. To obtain a good quality product with reasonable following issues are to be solved.

1.3.2.1 Light and Climate

These two factors play an important role in the growth of plants. Climate, rainfall, duration of day, altitudes and temperature are some of the other factors which will affect the cultivation plants. Various and different climatic conditions are required for different herbs and crops. Carbohydrate quantity will be reduced in leaves during a cloudy weather season because the photosynthesis process depends upon the daylight i.e. sunlight. Carbohydrates are the starting material for the bio-synthesis of the plant if amount of this is less, it will affect the amount of the secondary metabolites. Temperature changes also affect the chemical reactions in the plants. In reduced temperature the enzymatic reactions also will be slow down.

In this condition some middle products will accumulate in the cell and it will slow down the demand of the required production of the metabolites. This may give rise to automatic invention of toxic products inside the plant. (Example, (a) in cloudy or in the rainy days there will be low contents of alkaloids in leaves of Stramonium. (b) In aromatic plant like Lavender and Rose, the essential oil content is more on the dry sunlit climate. (c) Essential oil in Wormwood and Valerian is more in high temperature and dry sunlit weather. (d) Leaves of Belladonna yield three to four times more of alkaloids if it grown in sunny location than the shade.

Like this climatic and temperature changes can be affecting in plants like Cinchona, Lobelia, Peppermint and Opium poppy. In Nicotiana rustica, 20°C is the most favorable temperature for the nicotine production. The number of double bonds produced, in fatty acids are more at low temperature, than in the higher temperature. Kurchi bark will yield optimum alkaloid content at an atmospheric temperature of 25°C.

Natural disasters such as drought, flood, frost, snow, wind and hail are strange features found in the hilly region. From the sudden natural calamities we have to save our plants, for that serious preventive action should be taken by the governments. So, these situations should be considered duringr the cultivation time of the herbs.
Water holding and humidity of the soil depends upon the rainfall in the area where the plants are cultivated. Volatile production also depends on the rain fall. Heavy rain fall affects the roots, loss by the leaching and the production of volatile-oil and glycoside production in the family of Solanaceous plants.

1.3.2.2 Altitude and Latitude

Altitude or height plays an important role in the cultivation of medicinal plants. Sugar cane grows in a low altitude and coconut grows in a naval (marine) area. When elevation is reduced, the alkaloid content of *Lobellia inflate* and *Aconitum napellus* is also decreased. At very high elevation pyrethrum gives pyrethrin in good quantity and quantity.

In fat producing herbs latitude plays a vital role. A large amount of unsaturated fatty acids are produced by the sub-tropical plants. Coca butter and Palm oil (tropical plants) mainly contain saturated fatty acid and these plants are considered in tropical categories. Different categories of oils are produced from plants which are growing different latitude.

1.3.2.3 Allelopathy

This term allelopathy related to influence of the living organisms to each other in a frequent way. Growth encouragement or repression can be seen in various plants when other plants are growing side-by-side. It may be affect the maturation or shedding of the fruits and development of leaf. The allelopathic effects are transmitted among the plants by inhalation or exhalation and roots secretions. The change in the soil flora may depend upon the nature of organic compounds, humidity, fertilizer etc.

1.3.2.4 Nourishment or Nutrients

Nutrition has an imperative role on living organisms. For the production of drugs appropriate media with microorganisms are utilized and the evenness of lard depends upon nature of the hogs-food. According to the assortment of the rye-host plant, ergot illustrate that there is distinction of 30 % in alkaloid content. Other factors like humidity, temperature, appropriate light and inorganic salts affect the plant nutrition because play an important role in photosynthesis. So the nutritional requirements, in plants having a major role in secondary metabolites like glycosides, alkaloids or tannins production.

For peppermint oil harvesting is preferred on sunny days than overcast and rainy climate and the yield of the camphor is more in isolated trees of camphor than the trees.
which grow in the dense places. The rutine content is less in the plant of *Fagopyrum esculentum* which will grow in shade than in the light. Alkaloid content will be more in Belladonna leaves in the middle of the summer season because the growth and the light will be more during this time. In Digitalis leaves, the glycosides are more in the noon time than in the dark (night) time because of the availability of sugar in this afternoon time is more.

Plant population is a factor which will affect the availability of inorganic nutrient, water and light. Opium poppy will develop and grow in new seasonal or climatic conditions. Some plant constituents are lost elaborately when they are transferred to other place of different climatic conditions. *Astragalus* species which is a resource of tragacanath will stop the production of the gum when *Astragalus* is transferred to Northern areas from Mediterranean region. New plants are produced or selected from different strains. Thyme, digitalis purpurea and peppermint generate less active ingredients as it will grow in the low-lands. Aconitum gives less active principles, when the herb will grow in the mountains than in the low-lands. From these examples it may be concluded that, there are no specific regulations for the prediction of therapeutic activity of given species when it is relocated to a new environment.

### 1.3.2.4 Oxygen Minerals and Water

All living organisms require inorganic salts or ions for their proper biochemical growth development. Inorganic ions play numerous roles such as cell constituents, proper balance of elements and catalyst. The solubility of the inorganic ions depends up on the soil pH. For the proper cultivation of the medicinal herb it is important to check the soil status such as type of the soil, moisture retaining capacity, position of the micro and macro nutrients.

Various herbs need healthy growth and development conditions for the maximum yeild of the crop as well as the active constituents. During the transfer of a wild-plant to a nursery or a new cultivation territory, it is essential to supply them with a soil which is basically similar to its usual habitat. Rich soil provides a good amount of the active constituents from tramonium and Chamomile grow in acid type of soil. When the nitrogen or phosphorous supply is increased, the essential oil production also more in the case of coriander, anise, capsaicin in capsicum and fennel.
Active principles of herbs will not depend on the amount of the fertilizer which is supplied to or taken from the soil, when the inorganic ions are present in adequate quantity to prevent deficiency symptoms from developing. The amount of water in the soil will affect the therapeutic activity of the herb. On the dry ground Valerian produces more volatile oil than on a muddy soil. Mucilagenous substances act as an agent for water absorbing water and it will prevent the plant from drying. Decreased oxygen tension around roots can be seen in a swampy ground and it will affect the soil pH and mineral uptake.

1.3.2.5 Stage of Development

Aged and young plant organs yield drugs of different activity. The anthelmentic principle decreases while flower heads increase during growth. In pyrethrum flowers, the flower buds are more valuable than the expanded flowers, because they contain more active compounds, pyrethrins. The contents of ascorbic acid in rose hips (Rosa rugosa) are at its maximum (12%) in the last days of September. The contents of essential oils in American wormseed are highest during pollination. Rhubarb contains more anthraquinone in spring and during flowering than during winter. Young leaves of anthraquinone plants contain much more anthraquinone than the fully developed leaves. The camphor tree accumulates more and more camphor from year to year which will be highest at the period of 40 years. Aconite tuber contains 3 times more alkaloid in winter time when compared to summer.

1.3.2.6 Parasites

Like animals, plant has infectious diseases. The microbes and virus attack them, creating disturbances of the metabolites process of the host. Crops are reduced by plant infection. Henbane contains less alkaloid when attacked by rust. Peppermint cultures are affected by verticillium,. Valerian, fennel, belladonna, stramonium, etc. are also attacked mildews and rusts.

Virus infections of plants change the leaf and may hinder the development of other organs. Strains of various plants have been developed which are resistant to the more common infectious diseases. Streptomyces species used in the production of antibiotics are quite susceptible to attack by certain bacteriophages.
1.3.3 Preserving and Processing Procedures

Earlier the drugs were used mostly in fresh form. When the drugs were obtained from far away places, preservations of these products became a necessity. Several drugs lost their effectiveness on drying. *Cochlearia officinalis* on drying, its vitamin C content is destroyed spasmolytic properties of Thyme are lost in a dried sample.

1.3.3.1 Enzyme Activity

Enzymatic processes continue drying, but gradually the cell loses its control and power to coordinate this process. Several drugs containing glycosides lose activity during drying due to the actions of glycosidases. Normally, enzymes and substrates occur jointly in the cell, in the living cell they are spatially separated. In some plants, enzymes and substrate is found in different cell, e.g. the glycosides of mustard seeds. When the cells are crushed, the enzyme and substrate is united to react with each other. Fresh white squill bulb contains the cardioactive glycosides scillaren A and B. during preservations of this drug; a large proportion of the glycosides are destroyed.

Proscillaridin A and its anhydride, scillaridin, have weaker cardiac activity than scillaren A, the fresh bark of *Cascara sagrada* gives no reactions of anthraquinone, but after drying in the air for sometime, it forms red colour with alkali (brontrager reaction). Sometime desirable transformation takes place during drying. For example, vanillin is produced by hydrolysis of a glucoside through fermentation process in a vanilla bean. Cacao beans change in colour and flavor upon under going fermentation process, and the caffeine-tannin complex of tea is converted by enzymes in to free caffeine and oxidized tannin, phlobaphenes. If the enzymes are destroyed in these materials prior to drying, no changes occur.

Enzymes also cause deterioration in the activity of crude drugs. In opium, a proxidase is present which can cause a loss of up to 50% of the morphine of aqueous solution; this can be prevented by heating morphine to 70°C to destroy the enzyme. The enzyme present in the fresh latex of the opium poppy reduces the content of morphine up to 13%.
1.3.3.2 Browning

Fresh bark of Cinchona, Cascara sagarda and Cinnamon and fresh cola nuts are white to yellow inside, but darken to brown on drying. Many leaves and fruits become brown on drying and storage. Browning changes the taste, odour and activity. Browning is due to both enzymatic and non-enzymatic reasons and becomes faster in the presence of oxygen and at elevated temperatures. Polyphenol oxidase enzymes cause oxidation of polyphenols (tannins and flavonides) to relative quinines, which polymerize readily to yield dark-coloured compounds. The reaction is accelerated after there is damage to the tissue or after physiological injury, (freezing thawing or slow drying). This type of browning is inhibited by addition of ascorbic acid which reduces the formation of quinone.

The oxidation is highest in powdered drugs as the diffusion of oxygen into the inner portions of tissues is slow. Browning also occurs due to interactions of free sugar or dehydro ascorbic acid with free amino acid to form dark compounds. Addition of sulphur dioxide prevents browning, by eliminating carbonyl group.

Browning of dried leaves is due to transformation of chlrorophyll in to phaeochlorophyll in the presence of acidic cell sap. Bright green colour is retained in slight acidic conditions.

1.3.3.3 Oxidation, Evaporation and Polymerization

Unpleasant odour of henbane leaves and coriander fruits disappear on drying due to evaporations or transformations of flavouring substances. Volatile oils evaporate at high temperatures; therefore, drying in sunshine causes greater loss of volatile oil constituents than drying in the shade. Lavender, peppermint, sage and thyme loose about 10% of their oil on drying in the shade, but up to 24% if dried. Heat created during powdering and artificial heat used in the dying of crude drug destroys thermolabile constituents.

The oil constituents are first dissolved in water and then diffused through the cell wall in solution. Oxygenated compounds of essential oils, e.g. alcohols, aldehydes and carboxylic acids, are highly soluble in water and evaporate to a greater extent than the hydrocarbons. The drugs which carry oil glance on the surface lose oil faster than thicker organs. Peppermint with oil glance on the leaf surface loses about 40% of its oil in dried leaves.
1.3.3.4 Effect of Storage

Chemical changes in drugs occur most readily during storage and this process is known as ageing. In the presence of lipases, fats in seeds are hydrolysed to glycerol and fatty acids. In living cell, the consumption of glycerol and fatty acids is continued to prevent the accumulation of any of them, but in dead cell, fatty acids are deposited. Peroxides formed during this process may destroy therapeutic constituents. Storage of ergot causes rancidity and becomes inferior in quality. Therefore, powdered ergot must be stored only in the defatted form.

1.3.3.5 Enzymatic Process

The enzymes of the fresh drugs are not destroyed completely during drying. However, when the water content of the tissues is reduced below 5%, enzymatic reactions are reduced. Hygroscopic materials absorb humidity from the atmosphere, varying water content between 5 and 15%. Therefore, crude drugs, such as digitalis and senna leaves, should be stored in closed containers over dehydrating agents such as lime or calcium chloride. This type of storage is costly and difficult.

1.3.3.6 Oxidative Process

Drugs darken during storage due to oxidation reaction. Diffusion of oxygen into large pieces of drug requires a longer time than diffusion into the interior of small particles. Therefore, drugs containing phenolic compounds loose activity more rapidly when stored in powder forms. Many essential oils on exposure to air develop typical odour and becomes viscous. Addition of oxygen to double bonds gradually forms peroxides, aldehydes, ketones, alcohols and acids. In bitter almond, benzaldehyde is partially converted to benzoic acid on storing the oil in air. Peroxides form many secondary products in the oil in the presence of oxygen. Anethole of anise oil upon storage gives rise to ketone, aldehyde and acid. Therefore, the oil should be kept in completely filled bottles to eliminate the effect of oxygen. The bitter compounds of gentian roots, gentiopicrin, are oxidized in air to gentiamarin and $H_2O_2$ and the aglycones of these 2 glycosides are further oxidized to a larger number of products.

Post-mortem oxidation is used for the improvement of some drugs. The fresh bark of *Cascara sagarda* contains the active constituents in the reduced form,
(anthranols which and cause griping and nausea). During drying, a part of these compounds is oxidized to anthraquinones. Therefore, the drugs should be stored at least one year before used to destroy the gripping property. The oxidation proceeds faster at elevated temperatures. Therefore, the drugs should also be heated for one hour at 100°C. The colour of chrysarobin is changed from yellow to brown on storage in air and hence, its antiseptic property is reduced.

1.3.3.7 Rancidification

Spoilage of fats during storage is called rancidification. New compounds are formed which may change the consistency and therapeutic value of the fat. As inflamed areas of the skin are more sensitive to irritation, rancidified fats are undesirable for use in medicine. The main types of rancidity are acid rancidity, carbonyl compound rancidity and peroxide rancidity. The fat splitting enzymes, lipases, produce free acids in the presence of water causing acid rancidity. Natural fats contain small amounts of water in disperse form. Therefore, natural fats should be stored under anhydrous conditions. The activity of lipases can be inhibited by lowering the pH. The lipases are thermolabile, (ie. they are destroyed by heat). Many fats are exposed to steam for some time.

Oxidative rancidity is very important in the deterioration of fats. Microbes are developed when the fats contain water or proteins, eg. Lard and butter. By the action of microbes upon fat, methyl ketones having strong and disagreeable odour are formed. Unsaturated fats absorb oxygen in the presence of light, increasing the weight, becoming more viscous and finally a solid material. The iodine value of the fat is decreased. At elevated temperatures, oxygen adds unsaturated acid to form peroxides which on rearrangement splits the molecule between the carbons forming aldehydes of disagreeable odour. The reaction is autocyclic and started by UV light. Many substances eg. Fe, Cu, Co, Mn, and others accelerate the rate of oxidation. Such substances are called oxidants. Other substances retard the rate of oxidation and are known as antioxidants. Carotenes, gallic and ascorbic acids, pomiferin, tocopherol (vitamin E) and nordihydroguaiaretic acid are used as antioxidants.

1.3.3.8 Racemization

In natural products, most physiologically active compounds occur in I-form. Racemization in dextro-L form has only half the activity. The racemic forms of atropine and ergot alkaloids lose half of their alkaloidal activity.
1.3.3.9 Light

Many substances are affected by light. Santonin of levant wormseed turns yellow in
the light. The carotenoids of saffron is decolourized in the presences of light and essential oils
turn gradually dark and viscous. Vitamins A, B₂ and C are sensitive to light. The alkaloid
content of coca leaf, stramonium leaf and of veratrum root decreases faster when the drugs
are dried in light. (Mohammed 2004).

1.4 Parts of Plant

Either single or multiple parts of the same plant can be used as a source of
drug and hence it becomes necessary to know various parts of the plant scientifically. Natural
drugs may either constitute cellular or acellular organ of the plant. Cellular drugs are widely
known as organized crude drugs, where as, cellular drugs are known as unorganized crude-
drugs. Differences between organized and unorganized drugs are given as follows;

1.4.1 Organized Crude Drugs

As the term indicates these are organs of plants or animals and are made up of
cells or definite structure. These drugs are named as flowers, seeds, fruits, insects" etc.They
are solid in nature. Botanical or zoological terminology can be used to describe these drugs.
Microscopic characters are one of the most important criteria for the identification of
organized drugs. Examples: Digitals, cinchona, clove, fennel, jalap, ephedra, cochineal etc.

1.4.1.1 Leaves

There are several leaves, which useful in the practice of pharmacy. Leaves are flat,
thin, green appendages, connected to the stem containing, supporting and conducting strands
in their structures. Commercially, the word leaf includes compound leaf leaf and leaflets
(Kokate 2008).

Depending upon their biological sources, leaves, many a time, include the flowering
tops. In certain cases, the minimum percentage of active constituents is specified. The basic
difference between the leaf and leaflet is as shown in Table 2 follows
Table 2. Difference between Leaf and Leaflet

<table>
<thead>
<tr>
<th>SI.No</th>
<th>Leaf</th>
<th>Leaflet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In case of leaves, bud or branch is present in the axil.</td>
<td>It is absent in leaflets</td>
</tr>
<tr>
<td>2</td>
<td>Leaves are arranged spirally and they are solitary in nature</td>
<td>Leaflets are arranged in pairs</td>
</tr>
<tr>
<td>3</td>
<td>Leaves lie in different planes</td>
<td>Leaflets lie in the same plane</td>
</tr>
<tr>
<td>4</td>
<td>Leaves are generally symmetrical at the bases, e.g.: Digitalis, Bellodana, Vasaka.</td>
<td>Leaflets are asymmetrical at the base, e.g: Senna, Neem, Rose.</td>
</tr>
</tbody>
</table>

Apart from the normal characteristics i.e. their arrangement on the stems, their margin, apices, presence petiole, or absence of stipules etc leaves are characterized by certain diagnostic structures. Most of these diagnostic characters are microscopic such as stomata and stomatal index, trichomes, vein islet numbe, palisade ratio etc.

1.4.1.2 Collection of Leaves

The procurement of leaves depend on several factors and varies from one leaf to another. One should have thorough knowledge of the chemical constituents of leaves and the chemical changes which might take place in normal atmospheric conditions. Medicinal leaves are collected during the flowering season of plants, (when the plants reach maturity and they are photosynthetically most active). If the leaves contain volatile oil, irrespective of the other facts, they are usually collected when the plant is rich in volatile oil content. The weather and time of collection is also very vital for procurement of drugs. Dry weather with minimum humidity is ideal in most of the cases for plucking the leaves. Digitalis leaves are collected in dry weather, generally in the afternoon. Coca leaves are collected, when they are nearly ready to fall from the stems. The discoloration of leaves is undesirable and the leaves of substandard quality fetch less value in the market.
1.4.1.3 Preparation of the Leaves for the Market

The leaves after drying are graded as broken and entire leaves. Tossing and sieving are also done in many cases (Kokate 2008). The packing of leaves is likely to affect quality of the drug. In order to maintain the quality and potency of leaves, wherever necessary, leaves should be packed in air-tight containers protected from light and moisture.

1.4.1.3 Diagnostic Characters of Leaves

Apart from shape, size and color, leaves are characterized by several microscopic structures which help in their proper identification.

1.4.2.1 Barks

The secondary external tissues lying outside the cambium in root or stem of dicotyledonous plants are known as the bark. Botanically, bark is otherwise called as periderm. Periderm consists of three layers viz., cork (phellem); cork-cambium (phellogen) and secondary cortex (phelloderm). Commercially, bark consists of all the tissues outside the cambium. A young bark includes epidermis, cortex, pericycle and phloem. Barks are obtained from the plants by making longitudinal and transverse incisions through the outer layers followed by peeling. Barks may be obtained from stems or roots. Due to the excessive growth produced by the cambium and cork cambium, the external tissues get tangentially stretched or torn and hence, the epidermis is not found in the barks.

1.4.2.2 Characteristics of Barks

Barks exhibit several morphological and microscopical characters. The morphological characters need special attention, as they help in identification of the barks.

1.4.2.3 Shapes in Barks

The shape or form of the bark depends upon the method adopted for its preparation. It also depends on the type of incision made and the extent of any subsequent shrinkage of the tissues. When the bark is removed from the small branches due to shrinkage of the soft tissues, it tends to curve, forming concavity on the inner side, yielding curved pieces of bark, e.g: wild cherry and cassia. On the other hand if the concavity is on the outer side of the bark, it is described as re-curved, e.g: kurchi.

When the shrinkage of the tissues is to a greater extent and it forms deep trough or channel, it is called a “channeled bark”, e.g: ashoka, Cinchona ledgeriana and
cassia. In some cases, one edge of a bark covers the other to form quill, it is described as double quill e.g. Java cinnamon. Where, as sometimes one quill of a bark is put inside other quill to form a compound quill, e.g: cinnamon. Compound quill is a man-made shape of bark. It reduces the exposure of bark to atmospheric conditions and also saves the space in transport.

1.4.2.4 Fractures in Bark

The appearance shown by the transversely broken surfaces of the bark is known as fracture. It is, sometimes, useful in identification of barks. The types of the fractures are as follows. If the fractured surface is smooth, it is described as a short fracture (cinnamon and kurchi). If the exposed surface exhibits small rounded appearance, it is described as a granular fracture (wild cherry and cassia). When the broken surface shows the presence or uneven projecting points, it is called as splintery fracture, as seen in cinnamon. The presence of numerous fibers on the transversely broken surface is described as a fibrous fracture (cinchona). If the exposed surface shows the arrangements of layers (one over the other), it is described as a laminated fracture, as observed in quillaia.

The various characters shown by the barks on the outer, as well as the inner surface are also diagnostically important. Amongst these, the color, condition and presence of several growths (like lichens, mosses etc.,) are characteristic to each bark. The presence of lenticels and development of cracks are additional characters of bark. Outer surface of the bark shows presence of cracks and fissures, which are formed due to lack of elasticity or due to increase in girth of the trees. Fissures are usually deep. Wrinkles, which are seen on outer surface of the bark, result from shrinkage of inside the soft tissues. Furrows are troughs between wrinkles. Inner surface of bark shows characteristics such as striations, which are longitudinal and parallel lines. Transverse wrinkles present on inner surface are described as corrugations.

1.4.2.5 Methods of Collecting Barks

Barks are collected in a season when they contain maximum concentration of active constituent. Cinnamon is collected in rainy season, while wild cherry is collected in autumn. Following are the methods of collecting barks. **Felling method:** This is a very old method of collecting barks. There the tree is cut at base and bark is peeled out. This method is
not used at present commercially, since it causes total destruction of trees. **Uprooting method:** In this case, the roots of plant are dug out of soil and bark is stripped off from roots and branches. This method is applied for collection of root bark of cinchona in java. **Coppicing method:** In this method, the plant is allowed to grow for a definite period and then it is cut off at specific distance from soil. The stumps, which remain in ground, are allowed to send shoots, which develop further, independently yielding aerial parts. These new parts are cut off and bark is collected from shoots. As compared to other methods of collection of bark, this technique is more economical and less time-consuming. It is, therefore, the method of choice for collecting barks commercially. Cascara and cinnamon are collected by this method.

1.4.3 Stems

The stem is an ascending axis of the plant developed from the plumule. It consists of nodes, internodes and buds and it give rise to branches, leaves and flowers. The stem may be classified as aerial, sub aerial and underground. Depending upon the presence of mechanical tissues, the stems may be weak, herbaceous or woody.

**Weak stems:** When the stems are thin and long, they are unable to stand erect and hence may be one of the following types. **Creepers or prostate stems:** They grow flat on the ground without roots, e.g. grasses, gokharu, etc. **Climbers:** These are too weak to stand alone. They climb on the support with the help of tendrils, hooks, prickles or roots, e.g. Piper betel, Piper longum. **Twinners:** These coil the support and grow further. They are thin and wiry, e.g. Ipomoea and phaseolus. **Herbaceous or woody stems:** These are the normal stems and may be soft or hard and woody, e.g. sugarcane, ephedra tinospora etc.

1.4.4 Woods

In case of dicotyledonous plants, the tissues produced by cambium on inner side are collectively known as wood. Thus, it consists mainly of secondary xylem and smaller amount of other tissues. The cells forming these tissues are highly lignified. Commercially, two types of wood are available, heart wood (duramen) and sap wood (laburnum).

**Heart wood:** It consists of the innermost central region of dicot stem or root, which is non-functioning, non-living and dark colored part due to presence of several chemical substances like tannins, pigments, gums, resins, etc. It gives mechanical support,
e.g. sandal wood. **Sap wood**: It is the outer region of the wood, which is the only functional wood conducting water and food material to plant and is lighter in color, e.g. Quassia.

The transverse section of wood shows, annual rings, which represent seasons growth. The wood formed in spring is known as spring wood, while the wood formed in winter is known as autumn wood. In some cases annual rings are not marked due to absence of seasonal interruption and hence they are known as false annual rings. The wood, in which spring vessels are arranged more or less in a ring, is described as ring porous wood, e.g. oak.

When spring vessels are distributed uniformly, throughout whole spring wood, the wood is described as „diffuse porous wood“ e.g. quassia. The arrangement of fibers in wood also decides nature of the wood. When the fibers are straight and arranged parallel, resulting in a smooth and uniform fracture, the wood is described as straight grained- wood. If fibers in the wood are arranged at an angle roughly 30° the wood shall not break easily and result in an irregular and splintery fracture (*Kokate 2008*). It is, then, described to possess inter- locked grain as in guaiacum.

**1.4.5. Flowers**

The flower is a modified shoot meant for production of seeds. A typical flower consists of four different circles (whorls) arranged in a definite manner. A flower is built upon stem or pedicel with the enlarged end known as thalamus or receptacle. The four whorls of the flowers can be described as follows;

**Calyx**: It is the outermost whorl of flower and is generally green in color. The individual member of calyx is called sepal. **Corolla**: It is the second whorl of flower and is either white or bright colored. Each member of corolla is known as petal the number of petals varies with the type of flower. **Androecium**: It is the third circle of flower and constitutes the male part. The individual component is called as stamen and each stamen consists of filament, anther and connective. **Gynoecium**: This is the fourth circle of the flower and constitutes the female part. Each component is known as carpel or pistil and is made of stigma, style and ovary.

**1.4.5.1. Collection and Drying of Flowers:**

For pharmaceutical purposes, flowers are dried in shade, so as to retain their color and volatile oil content, if any. They are collected in dry weather and preferably during
Departmen of Pharamacy, JJT University, Rajasthan

morning hours. Saffron, pyrethrum, cloves, Artemisia chamomile rose, jasmine are the example of medicinal flowers.

1.4.6 Fruits

The phanerogams are said to be matured, when they reach the flowering stage. The ovules of the flowers, after fertilization, get converted into seeds, and the ovary wall develops further to form the protective covering over the seeds, which is known as fruit. In botany, this particular coating is also called pericarp. Pericarp consists of three different layers namely, epicarp, mesocarp and endocarp.

Epicarp: It is the outermost coating of the pericarp and may be thin, thick or woody. Mesocarp: A layer in-between epicarp and endocarp may be pulpy or made up of spongy parenchymatous tissue. Endocarp: The innermost layer of the pericarp may be thin, thick or even woody. It is not necessary that the fruits should have seeds. If the ovules do not fertilize, the seedless fruits are formed.

Depending upon the number of carpels present in the flowers and other structure, the fruits fall into following categories as 1) Simple fruits 2) Aggregate fruits and 3) Compound fruits. **Simple fruits:** These are formed from the single carpel or from syncarpous gynaecium. Depending upon the mesocarp, whether it is dry or fleshy, they are classified as dry fruits and fleshy fruits. Dry fruits are further classified into dehiscent and indehiscent fruits. **Aggregate fruits:** These fruits are formed from many carpels or apocarpous gynaecium. Examples:- Rasp-berry, Star-anise **Compound fruits:** In this particular case, many more flowers come together and form the fruits. Examples: - Long pepper, Mulberry, Pineapple.

**False fruits:** Sometimes, apart from the ovary the floral parts like thalamus, receptacle or calyx grow and form the part of the fruit and such a fruit is known as false fruit or pseudocarp. Following are few examples of pseudocarp in which other part of the flower forming important part of the fruit are shown in the bracket. Strawberry (thalamus), Cashewnut (Peduncle and thalamus), Apple (thalamus), Markingnu (peduncle) Pharmaceutical fruits differ from botanical fruits in the respect that, pharmaceutical fruits may or may not contain all the three layers, i.e. lemon and orange consist of only epicarp,
tamarind and bael consist of only mesocarp, while fennel and dill contain all the layers, enclosing seed.

1.4.7 Seeds

The seed is a fertilized ovule. It represents a condensed form of life and it is a characteristic of phanerogams. Parenchymatous body of the ovule known as nucleus contains embryo-sac surrounded by integuments (coatings). Seeds are characterized by the following structures,

**Hilum**: The point of attachment of seeds to stalk. **Micropyle**: the minute opening of the tubular structure, wherefrom water is provided for the germination of seeds. **Raphe**: raphe is described as longitudinal marking of adherent stalk of anatropous ovule. In the embryo-sac itself fertilization take place giving rise to embryo. Thus, seeds are characterized by the presence of three pass known as embryo, endusperm and seed coat. Endosperm is the nutritive tissue nourishing the embryo. Endosperm may or may not be present in the seeds.

Therefore, seeds are classified as follows. (1) **Endospermic or albuminous seeds**, (2) **Non-Endospermic or exalbuminous seeds**, (3) Perispermic seeds. **Albuminous or endospermic or seeds**: A part of the endosperm remains until the germination of seeds and is partially absorbed by embryo. It shows distinct presence of endosperm, e.g. colchicum, isapgol, linseed, nuxvomica, strophanthus etc. **Exalbuminous or Non-endospermic seeds**: During the development of seeds, the endosperm is fully absorbed by embryo and endosperm is not represented in the natural seeds, e.g: sun flower, tamarind, cotton, soybean etc. **Perispermic seeds**: Herein, the nucleus develops to such an extent that it forms a big storage tissue and seeds are found to contain embryo, endosperm, perisperm, and seeds coat; e.g: pepper, cardamom, nutmeg, etc

1.4.7.1 Special Features of Seeds

In some instances apart from regular growth of seeds, additional growth is visible in the form of appendages. It includes (a) **aril**: succulent growth from hilum covering the entire seeds, e.g.nutmeg (mace). (b) **arillode**: outer growth originating from micropyle, covering the seeds, e.g. cardamom. (c) **arista (awn)**: stiff-bristle like appendage with many flowering glumes of grasses e.g.stropanthus. (d) **varuncle**: It is warty outgrowth from
micropyle; e.g: castor, croton, and viola. (e) strophole: it is enlarged funicle. e.g: colchicum seeds.  (f) hairs: this is a type of out growth is seen in gossipium and calotropis. These appendages are found to perform special functions at times, for example hairs and awns of seeds help their dispersal.

1.4.8 Under-Ground Drugs

Underground drugs of the plant may be either root or it may be underground or sub-aerial modification of stem. The function performed by modified stem or root are basically different, but taking into consideration their occurrences as underground parts of the plants, they are put together irrespective of their function. Underground modifications of root and stem are of the following types: Roots, Rhizome, Tuber, Bulb and Corm

1.4.8.1 Roots

The roots are characterized by their downwards growth into the soil. They do not have nodes and inter nodes. Branching of roots arises from pericyclic tissues, the roots are covered by root caps or root heads. Commercially, there is no clear demarcation between roots and rhizomes. Rhizomes may contain good proportion of root or the roots may contain large amount of rhizomes, Hence the roots rhizomes and other underground parts of the plants are described together.

After collecting the roots and rhizomes it is necessary to prepare them carefully for the market. The roots and rhizomes have to undergo several operations for the preparation for market, which includes proper washing, drying and even in certain cases scrapping and coating. All these part can be distinguished from aerial parts and other underground parts of their plant by specific characteristics.

Examples: Rauwolfia, Ashwagandha

1.4.8.2 Rhizomes

The rhizomes grow horizontally under soil. They are thick, fleshy and characterized by presence of nodes, inter nodes and scale leaves. They also possess bud in the axil of scale leaves. Adventitious roots may also be present on lower surface of the rhizomes; the rhizomes may be branched and may serve as to storage organs.

Examples for the rhizomes are Ginger, Dioscorea, Turmeric, Rhubarb etc.
1.4.8.3 Tubers

The tubers are characterized by presence of *eyes* from vegetative buds, which grow further and develop into a new plant. Tubers are swollen underground structure of plant. Adventitious roots are absent in tubers. Tubers are organs of storage, as well as, propagation.

Examples of tubers are Potato, Aconite, Dioscorea etc

1.4.8.4 Bulb

The bulb is a specialized underground shoot. The food material is stored in fleshy scales, which overlap the stem. The buds are present in axils of the scales and few of them develop in spring seasons at the expense of stored food material in the bulb. The reserve food material formed by leaves is stored at their bases and new bulbs are produced in subsequent year. The bulb is an organ of prennation as well as vegetative propagation.

Examples of bulbs are Garlic, Onion, Squill etc.

1.4.8.5 Corm

The corms are also the underground modification of stems; generally they are stout and grow in a vertical direction. They bear bud in axil of the scale leaves and these buds then develop further to form new plant. Adventitious roots are present at the base of the corm; the growth of corm is sympodial. The examples of corm are saffron and colchicum. Sub-aerial modifications of stems; these include; runner, stolon, offset and sucker.

**Runner:** The runners have the specialty of creeping on ground and rooting at nodes, auxiliary buds are also present in case of runner. Straw-berry and pennywort are examples of runners. **Stolon:** The stolons are lateral branches arising from base of the stems, which grow horizontally. They are characterized by presence of nodes and inter nodes. Few branches growing above the ground develop into new plant. The examples of stolens are glycyrrhiza, arrow root and jasmine.

**Offset:** These are originated from axil of the leaf as short and thick horizontal branches. They are also characterized by presence of rosette type of leaves and a cluster of roots at their bottom. Offset is shorter and stouter than runner. e.g; Aloe, Valerian **Sucker:** The suckers are lateral branches developed from underground stems. Suckers grow obliquely upwards and give rise to a shoot, which develop further into new plants; they are
characterized by the presence of scale leaves. Examples of suckers are mentha species pineapple, banana etc.

The term entire organism is used to denote the utility of major portion of a plant or animal as a drug. Plant drug categorized as entire organisms are even called as herbs, which means all the aerial parts of the plant, including leaves, flowers, seeds and smaller stems. this does not include the main axis of the stem. thus, belladonna, cannabis, datura kalmegh, chirata and lobelia, are observed under this type. Ergot represents dried sclerotium of the fungus, where as ephedra constitutes the stem portion of the plant. These two drugs are also classified as entire organisms.

1.4.9 Unorganized Crude Drugs

These are derived from parts of plant or animal by some process of extraction and followed by purification, if necessary, e.g. juices, extracts, resins, etc. These are solid, semisolid or liquids in nature, e.g. oils, gums, balsams etc. Unorganized drugs are commonly described by their physical characters only. The description for some of them is given below.

1.4.9.1 Gums and Mucilage

Gums are translucent and amorphous substances, produced by plants. Gums are pathological products and are produced only when the plant is growing under un-favorable conditions or is injured. Thus, they are the abnormal products (not produced during the normal plant metabolism) of plant growth. Gums are produced outside the cells of plant by the process known as “Gummosis”. Gums are soluble or partially soluble in water, they are insoluble in alcohol and in the most of the organic compounds.

Gums are in the form viscous adhesive solutions with water, either by swelling or due to absorption. Aqueous solution of gum is usually laevorotatory. Gums are plant hydrocolloids and may be anionic or non-ionic polysaccharides. On hydrolysis, (acidic hydrolysis or prolonged boiling with water), gum yield sugar and uronic acids which form salts with calcium and magnesium.

The uronic acids are glucoronic acids or aldobionic acid. Pharmaceutically important gums are gum acacia, tragacanth gum, karaya gum, ghatti and guar gum. Mucilage are also plant product, similar to gums and regarded to be the normal products of plant growth. Mucilages are produced inside the cells of the plant. Mucilages form slimy
masses with water, but do not dissolve. Mucilages are esters of sulphuric acid, where in ester group is a polysaccharide complex.

1.4.9.2 Resins and Resin Combinations

**Natural resins:** The non-uniform physical and chemical nature of these substances makes them difficult to be defined. They are obtained from plant, as well as animal sources. Plant resins are natural or induced exudates. They are un-crystallisable solution of semi viscous materials found in plants and are the end products of plant metabolism. Very often they are clear, translucent yellow or brown materials insoluble in water and soluble in most of the organic solvents like alcohol, chloroform, benzene etc. Upon heating the soften melt and finally burn with a sooty flame. On storage, some of them darken in colour due to the chemical changes. Chemically the natural resins are organic compound without nitrogen. They represent various groups like acid alcohol esters and few others. Examples podophulium resin, jalap resin, colophony etc.

**Oleo-resins:** When the natural plants resins are accompanied with the volatile oil in homogenous form. They are known as oleo resins Canada balsams and copaiba are suitable Examples of oleo resins ((one should not compare these with prepared oleo resins which are prepared by percolating drugs containing volatile oil and resin together. the e.g of these type are capsicum and ginger oleo resins). **Oleo-gum resins:** These are the combination of gum, volatile oils, and resins. Sometimes, they also contain other substances like enzymes e.g.myrrh, guggul and asafoetida. **Balsams:** Aromatic resinous substances of plant origin containing balsamic acids (i.e. benzoic acids and cinamic acids) are known as balsams. Neither Canada balsams nor balsams of copaiba contain any balsamic acids and hence they are not balsams in real sense, e.g: balsam of tolu, benzoin, storax and balsam of Peru.

1.4.9.2.1. Methods of Preparation of Resins

Depending upon the occurrence of resins in plant, various methods for their preparation and adopted. These pathological products are collected by making incisions either into bark or trunk of the tree. **Dried juices:** The juices are obtained from fleshy leaves. (Aloe) or from stems of the trees (kino). in all cases incisions are made to respective part of the plant and juice coming out is collected and dried. Various methods are used to dry the
Latices: The latex is produced contained in special secretary tissues of certain plants. It is usually a while aqueous suspension. Where in microscopical, the small particles of oil globules are suspended. These natural suspensions of milky consistency may proteins, sugars, mineral and alkaloids salt in the true solution, where as gum starch and resins in suspended form. e.g are commercially important latices are rubber a chicle gum, while pharmaceutically important, latices are opium, papain and gum percha.

Extracts: The extracts covered under crude drugs differ from galenical extracts. The extract of pharmacognostic origin consists of extracting the parts of t plants with water followed by concentration which pharmaceutical preparations known as extracts are prepared by using alcoholic solutions and adjusting the product to the standard strength. Agar, sodium alginate and catechu are few extracts of plant origin (Kokate 2008).

1.5 Cultivation of Medicinal Plants

Through several countries in the world have a rich heritage of herbal drugs? Very few can put claim for their procurement only from cultivated species. It is recently that some of these drugs have been subjected to systematic cultivation based on modern scientific information. Our reliance on wild form of crude drugs and the lack of information of, sound cultivation technology have resulted in gradual depletion of raw material from wild sources. Even though, cultivation of medicinal plants offers wide spectrum of advantages over their wild sources, it may be an uneconomical proposition for certain types of crude drugs which occur abundantly in their natural habitat e.g. nuxvomica, acacia, myrobalan etc.

On the other hand, crude drugs like cardamom, clove, Indian hemp, poppy latex, tea, cinchona, ginger, linseed, isabgol, Ceylon, cinnamon, saffron, peppermint, fennel, etc. are obtained from cultivated plants. The cultivation of vegetable drugs involves convergence of various factors from agricultural and pharmaceutical here, such as soil, climate, rainfall, irrigation, altitude, temperature, use of fertilizers and pesticides, genetic manipulation and biochemical aspects of natural drugs. When all such factors are precisely applied, the new approach to scientific cultivation technology emerges out. The advantages of cultivation may be briefly summarized as follows:

1. It ensures quality and purity of medicinal plants. Crude drugs derive their utility from chemical contents in them, if the uniformity is maintained in all operation during the
process of cultivation. Drugs of highest quality can be obtained from cultivation of rhizomes, demand an adequate quantity of fertilizers and proper irrigation. Systematic cultivation results in raising a crop with maximum content of volatile and other constituents. Examples of ginger, turmeric and liquorice can be cited to illustrate this point.

2. Collection of crude drugs from cultivation of plants gives a better yield of therapeutic quality. If the collection of crude drugs for market is done from cultivated plants by skilled and experienced personnel, the high yield and therapeutic quality of drugs can be maintained, (e.g. collection of latex from poppy capsules and oleo resins from pinus species if done by experienced persons can result in better yield of crude drugs).

3. Cultivation ensures regular supply of crude drugs. Cultivation is a method of crop planning. Planning crop cultivation regularizes its supply and as a result the industries depend upon the crude drugs do not face the problems of raw materials.

4. The cultivation of medicinal and aromatic plants also leads to industrialization. The cultivation of cocoa and coffee in Kerala has given rise to several cottage and small scale industries. The cultivation of cinchona in west Bengal has led to the establishment of the cinchona alkaloid factory near Darjeeling.

5. Cultivation permits application of modern technological aspects such as mutation, polyploidy and hybridization.

1.5.1 Factors Affecting Cultivation

Cultivation of medicinal and aromatic plants takes cognizance of plant habitats and climatic requirement for the favorable growth. Factors affecting the cultivation methods are Altitude, temperature, humidity: and water availability (rain fall or irrigation).

**Altitude:** Altitude is a very important factor in cultivation of medicinal plants. Tea; cinchona and eucalyptus are cultivated favorably at an attitude of 1000- 2000 meters. e.g. , Camphor at 1500m-2000m, clove up-to 900 and Cardamom at 600- 1600m. **Temperature:** is another factor affecting the growth of a plant. Excessive temperature as well as frost affects quality of medicinal plants adversely. Examples are Cinchona 60-75 °C, Coffee 55-70 °C. **Rain fall or Irrigation:** Except the xerophytic plants like aloe, acacia and few others. Most
of the plants need either proper arrangements for irrigation or sufficient rainfall for their favorable development.

1.5.2 Methods of Plant Propagation

Medicinal plants can be propagated by two usual methods as applicable to non-medicinal plants or crops. Sexual method (seed propagation), where the plants are raised from seeds and such plants are known as seedling.

1.5.2.1 Advantages

Seedlings are long lived and bear more heavily, plants are sturdier. Seedlings are comparatively cheaper and easy to rise. Propagation from seed has been responsible for production of some chance seedling of highly superior merits which may be of great importance to specific products, orange, papaya etc. In case of plants where outer vegetative methods cannot be utilized, propagation from seeds is the only method of the choice.

1.5.2.2 Limitations

Generally seedling trees are not uniform in their growth and yielding capacity as compared to grafted trees. They require more time to bear as compared to grafted plants. The cost of harvesting, spraying of pesticides etc is more as compared to grafted trees. It is not possible to avail modifying influence of root stocks on scion, as in case of vegetative propagated trees.

For propagation purpose the seeds must be of good quality, they should be capable of high germination rate, free from diseases and other insects and free from other types of seeds. The germination capacity of seeds is tasted by rolled towel test and excised embryo test. If the seeds are not to be germinated in near future they should be stored in cool and dry place to maintain their germinating power. Long storage of seeds should be avoided. Before germination sometimes a chemical treatment is given with stimulants like gibberellins, cytokines, ethylene potassium nitrate or sodium hypochlorite. Many freshly harvested dormant seeds germinated better after soaking in potassium nitrate solution. Thiourea is used for those seeds with do not germinate in dark or at high temperature.
1.5.2.3 Methods of Sowing Seeds

Numerous methods of sowing the seeds of the medicinal plants are in practise;

**Broadcasting method**: If the seeds are extremely small the sowing is done by broad casting method. The seeds are scattered freely in well prepared soil for cultivation. The seeds only need raking. If they are deeply sown in soil it may not germinated. **Dibbing**: When the seeds are average size and weights are available, they are sown by placing in the holes, number of seeds to be put in holes vary from 3-5 depending upon the vitality. (In case of fennel 4-5 fruit of fennel are put in a single hole kept, suitable distance between two holes, where as in the case of Castor only 2-3 seeds are kept). **Miscellaneous**: Many times seeds are sown in nursery beds, the seedling thus produced are transplanted to farm for further growth such as cinchona, cardamom, capsicum etc.

1.5.2.3.1 Special Treatment of Seeds

To enhance the germination special treatments some seeds may be given special treatment such as soaking the seeds in water for a day. (e.g. castor seeds and other slow germinating seeds) where as seeds are soaked in sulphuric acid. e.g. henbane seeds.

1.5.2.4 Asexual methods

In case of asexual methods of vegetative propagation the vegetative part of a plant, such as stem or root. is placed in such an environment that is developed into a new plant.

1.5.2.4.1 Advantages of Asexual Methods

There is no variation between the plant growth and plant from which it is grown. There is uniform growth and yielding capacity. In case of fruit trees, uniformity in the fruits quality makes harvesting and marketing easy. Seedless varieties of fruits can only be propagated vegetatively e.g., grapes, lemon. Plants start bearing earlier as compared to seedling trees. Budding or grafting encourages diseases resistant varieties of plants. Modifying influence or roots stocked on scion can be availed inferior or unsuitable varieties can be over looked.

1.5.2.4.2 Disadvantages of Asexual Methods

These are not vigorous in growth and are not long lived. No new varieties.

Natural method of vegetative propagation: It is done by sowing various parts of plants in well
prepared soil. (Bulbs-squill, garlic, Corms-colchicum, saffron, Rhizomes-ginger, turmeric, Runners-pepper, Suckers-banana, Stolons-arrow-root).

1.5.2.5 Artificial Method of Vegetative Propagation

Any method by which plantlets or seedling are produced from vegetative part of the plant by using some technique or process is known as artificial method of vegetative propagation.

**Cutting:** Soft wood cutting (berberry), Semi hard wood cutting (e.g. citrus), Hard wood cutting – (orange, rose), Root cutting (brahmi), Leaf cutting (bryophyllum)
**Layering:** Simple layering (guava), Serpentine layer (jasmine), Air layer (mango, cashew nut), Grafting: Whip grafting (apple, rose), Side grafting (sapota), Approach grafting (guava), Stone grafting (mango).

1.5.2.6 Method of Micro Propagation (Tissue Culture)

It is a novel method for propagation of medicinal plants. In micro propagation, the plants are developed in artificial media under aseptic condition from the fine pieces of plants like a single cells, callus, seeds, embryos, root tips, shoot tips, pollen grains etc. They are also provided with nutritional and hormonal requirements.

1.5.2.6.1 Preparation and Type of Nursery Beds

For various genuine reasons some seeds cannot be sown directly into the soil i.e. very small size (isapgel) high cost poor germination rate and long germination type (coriander) under such circumstances seeds are grown into the nursery beds which not only is economical but one can look after the diseases during germination period. Small size of buds can be irrigated conveniently along with the fertilizers as and when necessary.

1. Flat bed method
2. Raised bed method
3. Ridges and furrow method
4. Ring and basin method

1.5.2.7 Methods of Irrigation

Water is essential for any type of cultivation after studying the availability and requirement of water for a specific crop one has to design his own irrigation system at the
reasonable cost. Following methods of irrigation are known traditionally in India. The cultivation has an option after giving due consideration to the merits and demerits of each.
1. Hand watering: economical and easy to operate.
2. Flood watering: easy to operate
3. Boom watering: easy to operate, but restricted utility.
4. Drip Irrigation: systematic and easy to operate
5. Sprinkler irrigation: costly, good result.

1.5.3 Plant Growth Regulators

Plant growth regulators are the organic compounds other than nutrients which affect the morphological structure and physiological process of plants in low concentration, phyto-hormones or plant hormones are naturally occurring in growth regulators, which in low concentrations control physiological processing of plants. More commonly, the term plant growth regulators are used, because it induces both the negative and the synthetic substance, which modify the plant growth. As the native plant growth regulators, five major kinds of substances are reported, viz. All of them excepting ethylene and abscisic acid are multiple forms of endogenous plant growth regulators. In general the plant growth regulators or substances serve role in regulating cell enlargement, cell division and cell differentiation. They are employed in seed treatment to achieve early growth, development, quality improvement like protein level and amino acid balance etc.

1.5.3.1 Auxins

Auxins are a general term used to indicate substance that promotes elongation of coleoptiles tissues. IAA is the principle and other natural auxins are indole-3-acetonitrate (IAN) and 4-chloroindole. The synthetic auxins include indole-3-butric acid (IBA). Auxins are involved in different growth processes in plants like inter-node elongation, leaf growth, initiation of muscuar tissues, cambial activity, pollination, fruit growth, apical dominance, physical and chemical properties in leaf abscission and inhibition of lateral buds. IBA and NAA in combination are used in rooting and cutting. IBA has shown promising results to induce in cutting cinchona and coffee (Kokate 2008). The addition of different auxins like IAA, NAA and 2, 4-D in tissue culture of ergot has led to increase in aldole alkaloids.
1.5.3.2 Gibberllins

They are class of endogenous plant growth regulators, and at present over 50 gibberllins are known. About 40 of them occurring in green plants, while others are present in some fungi. The commercial formulations of gibberllins are used to currently used for promoting vegetative and fruit growth, breaking dormancy and flower initiation. The thorough research on gibberellins carried out in Japan, United States and Great Britain has shown that gibberellin A is actually a mixture of at least 6 gibberllin referred to as GA₁, GA₂, GA₃, GA₄, GA₇ and GA₉. GA₃ is termed as gibberlic acid.

All of them are the derivative of gibbane ring skeleton. GA has not yet been synthesized but can be produced on commercial scale by large scale fermentation on commercial scale. The angiosperms, gymnosperms, ferns, fungi and bacteria contain several forms of gibberellins but no single plant contains all of them together. The effect of gibberrellins on cell division is for increase in cell size similar to those auxins. It is observed that gibberellins are more impact on plants, while major auxins effects are on excised organs.

The application of gibberrellins is extended to various medicinal plants. The dose of gibberrellins in lower dose has shown increased yield of digitalis glycosides per shoot. The hormone tried with leaf and root culture of digitalis, showed higher production of digioxin. The mechanism of action of gibberellins acid appears mainly into induced activity of gluconeogenic enzymes during early stage of seed germination and this specificity ensures a rapid conversion of lipid to sucrose which is further used in supporting growth and development of embryonic axis to a competent root and shoot system. They are also involved in mobilizing seed storage reserves during germination and seedling emergence.

1.5.3.3 Cytokinins

These are either natural or synthetic compounds with significant growth regulating activity. Zeatin has effect on cell division and synthetic cytokinins are useful in promoting lateral development and inhibition of leaf scnescence. Cytokinins influence a board spectrum of physiological process in plants like promotion of cell division the other activities exerted are participation in orderly development of embryos during seed development influencing the expansion of cell in leaf discs and cotyledons delaying breakdown of chlorophyll and degradation of proteins in ageing leaves.
The naturally occurring cytokinins are Zeatin N⁶ dimethyl amino purine and N⁶-isopentenyl amino purine. Cytokinins are reported to increase marginally sennoside content in Tinnevelly senna leaves and also enhance the grey white of shoots. In opium, they cause formation of elongated capsule and reduction of alkaloid content. Kinetins are reported to play the role in nucleic acid metabolism and protein synthesis. In plant metabolism it is proposed that some t-RNA contain cytokinins like activity. They have an action on some enzyme responsible for formation of certain amino acids.

1.5.3.4 Ethylene

It is a simple organic molecule present in the form of volatile gas and shows profound physiological effects. It present in ripening fruits, flowers, stems, roots, seeds and tubers. It is present in very less quantity in plants normally about 0.1ppm. its quantity is increased in local areas during the time of growth and development. Ethylene is produced by incomplete burning of carbon rich substance like natural gas coal and petroleum. Ethylene shows a broad array of growth responses in plants which include fruit ripening leaf abscission, stem swelling, leaf bending and inhibition of stem and root growth. It is commercially used for promotion of flowering and fruit ripening, induction of abscission.

1.5.3.5 Abscisic Acid (ABA)

The physiological activities in plants like retaining or shedding of different organs like leaves, stems, flowers and fruits have led to finding of natural growth inhibitory. In an inhibitory way ABA interacts with other plant growth substances. It inhibits the GA-induced synthesis, alpha amylase and other hydrolytic enzymes. During maturation AB accumulates in many seeds and helps in seed dormancy. ABA serves an important role as potential anti transparent by closing the stomata when applied to leaves.

A number of other synthetic growth inhibitors and retardants are reported are maleic hydrazide, daminozide and chromic chloride, S, S, S-tributyl phosphorothioate, chlorophoneum etc. However commercial use of this compound is yet to be reported. A group of synthetic substances called morphantins is potent inhibitor of auxin transport, causing tropic response reduction of apical dominance and promoting lateral growth. Morphactins include chloroflurecol methyl, flurecol- butly and TIBA.
1.5.4 Green Houses

It is an emerging field of agricultural technology for protecting the crops against un-favorable environments or for modifying the natural environment, so as to yield good quality and quantity of plant crops. Advantages are the following:

- As much as 4-5 crops can be grown per annum by using green house due to availability of required plant environmental condition
- It helps in increasing the productivity of the crop
- Since the growing area is enclosed in green house pest and diseases can be controlled effectively.
- Percentage of seed germination is very high.
- Since the plant is grown under suitable environment, high quality product is produced.
- Green houses can be used for acclimatization of plantlets developed by tissue culture technique.
- Various types of growing media can be used in green house effectively.
- Schedule for agriculture crop production can be planned according to the market needs.
- It helps in maintaining the international standards required for export purposes.

By the application of artificial intelligence techniques and computers automations of irrigation fertilizers and plant protections chemicals are possible in green house.

1.6 Collection and Processing of Medicinal Plants

After cultivation of the plants they are subjected to another process known as collection. Following the collection of the crude drugs they are required to be processed prior to marketing. The reason for preparation of drug is to stabilize them during transport and storage in order to ensure the absence of foreign organic matter and substitutes. Market preparations of crude drugs are also taken care of pharmaceutical elegance. While preparing drug for commerce several methods is adopted to meet the standard pharmacopoeial requirements, usually these methods include proper methods of collection and harvesting, drying and garbling. Sometimes coating and bleaching are also necessary for converting the
drugs into suitable form for the market, while doing so it should be observed that neither the action of the drug is lowered down nor it is changed, due to the additives used in the process.

1.6.1 Collection

Irrespective of the type of crude drug and area of collection, there cannot be two opinions that the drugs are collected suitably when they contain maximum concentration of active constituents. The advantages for existing environmental conditions are also taken into consideration while collecting the crude drugs. The drug which constitute leaf and the flowering tops of the plants are collected just before their flowering stage (maturity), [e.g: senna, digitalis, vinca, belladonna etc], while the leaves of aloes are collected when they are sufficiently thick. Flowers need to be collected just before pollination or many a times before they are full expansion, [e.g. saffron, clove buds etc], during morning hours, barks are generally collected in spring or early summer when cambium is active, as it easy to detach them from the stem.

Sometimes they are collected in autumn (wild cherry) or in rainy seasons (cinnamon). Three different methods for collecting barks are 1) Felling, 2) Uprooting 3) coppicing. In Felling method the trees are cut at base and bark is peeled out. In Uprooting technique, the roots are dug out, and bark is skipped off from roots and branches. In Coppicing method, the plant is allowed to grow for a definite period and then it is cut off at specific height from soil. The stumps which remain in ground are allowed it send shoots, which develop further, independently yielding aerial parts. These new parts are cut off and bark is collected from shoots. As compared to other methods of collection of the bark, this technique is economical and less time consuming. It is, there for, the method of choice for collecting barks commercially. Cascara and cinnamon are collected by this method.

The fruits are collected depending upon the parts of fruits used. They are collected either ripe or half ripe, but fully grown. Example: - cardamom fruits are collected before their dehiscence; bael and tamarind, after their maturity, while caraway fennel and coriander are collected, when they are fully ripe. The roots are collected in spring before the vegetative process stops. Usually, their roots are sliced transversely or longitudinally to facilitate drying. Rhizomes are collected when they store ample of reserve the food material and also contain the maximum content of chemical constituents. The un-organized drugs such
as resins, gums, latices are collected, as soon as, they ooze out of the plant. Acacia gum is collected 2-3 weeks after making incisions on the bark of the tree and when it is sufficiently hard. Opium and papaya latices are collected after coagulation of latex. Turpentine oleo resin and balsam of Peru are collected when the plant is about 8-10 years old.

1.6.2 Harvesting

Harvesting is an important operation in cultivation technology, as it reflects upon economic aspects of the crude drugs. An important point which needs attention over here is the type of drug to be harvested and the pharmacopoeial standards which it needs to achieve. Harvesting can be done efficiently in every respect by the skilled workers. Selectivity is of advantage, in that the drugs other than genuine, but similar in appearance can be rejected at the site of collection. It is, however laborious job and may not be economical. In certain cases it cannot be replaced by mechanical means. e.g.: digitalis, tea, vinca and senna leaves.

The underground drugs like roots rhizomes tubers etc, are harvested by mechanical devices, such as diggers or lifters. The tubers or roots are thoroughly washed in water to get rid of earthy matter. Drugs which constitute all aerial parts are harvested binder for economic reasons. Many times, flowers, seeds and small fruits are harvested by special devices known as seeds stripper. the technique of beating plants with bamboos is used in case of cloves. The cochineal insects are collected from branches of cacti by brushing. The sea weeds producing agar are harvested by long handled forks. Peppermint and spearmint are harvested by normal method with mowers, where as fennel, coriander and caraway plants are uprooted and dried. After drying, either they are thrashed and beaten off or the fruits are separated by winnowing. Sometimes, reaping machines are also used for their harvesting.

1.6.3 Drying

Before marketing a crude drug it is necessary to process it properly, so as it to preserve it for a longer time and also acquire better pharmaceutical elegance. This processing includes several operations or treatments, depending upon the source of the crude drug (animal or plant) and its chemical nature. Drying consists of removal of sufficient moisture content of crude drug, so as to improve its quality and make it resistant to the growth of microorganism. Drying inhibits partially enzymatic reactions, drying also facilitates
pulverizing or grinding of a crude drug. In certain drugs, some special methods are required to be followed to specific standards e.g. fermentation in case of *cinnamomum zeylanicum* bark and gentian roots. The slicing and cutting into smaller pieces is done to enhance drying, as in case of glycerrihiza, squill. The flowers are dried in shade so as to retain their color and volatile oil content. Depending upon the type of chemical constituents, method of drying used for a crude drug are natural and artificial drying methods.

1.6.3.1 Natural Drying (Sun Drying)

In case of natural drying, it may be either direct sun drying or in the shade. If the natural color of the drug (digitalis, clove, senna) and the volatile principles of the drug (peppermint) are to be retained, drying in shed is preferred. If the contents of the drugs are quite stable to the temperature and sunlight, the drugs can be dried in sunshine (gum, acacia, seeds, and fruits)

1.6.3.2 Artificial Drying

Drying by artificial means includes drying the drugs in tray dryers, vacuum dryers and spray dryers. **Tray Dryers:** the drugs which do not contain volatile oil and are quite stable to heat or which need deactivation of enzyme, are dried in tray dryers. In this process, hot air of the desired temperature is circulated through the dryers and this facilitates the removal of water content from the drug (belladonna roots, cinchona bark, tea and raspberry leaves and gums are dried by this method). **Vacuum Dryers:** the drugs which are sensitive to higher temperature are dried by this process. e.g.: Tannic acid and digitalis leaves. **Spray Dryer:** Few drugs which are highly sensitive to atmospheric conditions and also to temperature of vacuum drying are dried by spray drying method. The technique is followed for quick drying of economically important plant or animal constituents, rather than the crude drugs (e.g. spray drying is done in papaya latex, pectin, tannins etc).

1.6.4 Garbling (Dressing)

The next step in the preparation of crude drug for market after drying is garbling. This process is desired when sand, dirt and foreign organic parts of the same plant, not constituting a drug are required to be removed, this foreign organic matter is removed by several ways available and practicable at the sight of the preparation of the drugs. If the extraneous matter is permitted in the crude drugs, the quality of the drugs suffers and at
times, it does not pass pharmacopoeial limits. Excessive steam in case of lobelia and stramonium need to be removed, while the stalks, in case of clove are to be detected. Drugs constituting rhizomes need to be separated carefully from roots and rootlets and also stem bases. Pieces of iron must be removed with the magnet in case of castor seeds before crushing and by shifting. In case of vinca and senna leaves, pieces of bark should be removed by peeling as in gum acacia.

1.6.5 Packing

The morphological and chemical nature of drug, its ultimate use and effects of climatic conditions during transportation and storage should be taken into consideration while packing the drugs. Aloe is packed on goat skin, colophony and balsam of Tolu is packed in kerosene tins while asafetida is stored in well closed container to prevent loss of volatile oil. Cod liver oil, being sensitive to sunlight should be stored in such containers which will not have effect of sunlight where as, the leaf drugs like senna, vinca and are pressed and baled.

The drugs which are very sensitive to moisture and also costly at the same time are given special attention while packing, (e.g., digitalis, ergot and squill). Squill becomes flexible ergot becomes susceptible to the microbial growth, while digitalis loses its potency due to decomposition of glycoside (Kokate 2008). It brought in contact with excess of moisture during storage. Hence the chemicals which absorb excessive moisture from the drug are incorporated in the containers colophony needs it to be packed in big masses to control auto oxidation .Cinnamon bark which is available in the form of quills, is packed one inside the other squill, so as to facilitate transport and to prevent volatilization of oil from the drug. The crude drugs like roots seeds and others don’t need special attention and are packed in gunny bags, while in some cases bags are coated with polythene internally. The weight of certain drugs in lots is also kept constant e.g.: Indian Opium

1.6.6 Storage of Crude Drugs

Preservation of crude drugs needs sound knowledge of their physical and chemical properties. A good quality of the drugs can be maintained if they are preserved properly. All the drugs should be preserved in well closed and possibly, in the filled containers. They should be stored in the premises which are water proof, fire proof and rodents proof areas. Number of drugs absorb moisture during their storage and become
susceptable it to the microbial growth, some drugs absorb moisture to the extent of 25% of their weight the moisture not only increases the bulk of the drug, but also causes impairment in the quality of crude drug. The excessive moisture facilitates enzymatic reactions resulting in decomposition of active constituents, e.g. Digitalis leaves, wild-cherry bark, gentian and ergot receive mould infestation due to the excessive moisture.

Radiation due to direct sunlight also causes destruction of active chemical constituents e.g. ergot, cod liver oil and digitalis. Form or shape of the drug also plays important role in preserving the crude drugs. Colophony in the entire form preserved nicely but if stored in powered form it gets oxidized or loses solubility in petroleum ether. Squill when stored in powered form becomes hygroscopic and rubbery mass on prolonged exposure to air. Apart from protection against adverse physical and chemical changes the preservation against insect or mould attacks are also important. Different types of insect nematodes, worms, moulds and mites infest the crude drugs during storage.

The common fumigants used for storage of crude drugs are methyl bromide, carbon dilute sulphide and hydrocyanic acid. At times, drugs are given special treatment such as liming of ginger and coating of nutmeg. The temperature is also very important factor in the reservation of the drugs, as it accelerates several chemical reactions leading to decomposition of the constituents. Hence most of the drugs need to be preserved at a very low temperature. Small quantity of crude drug could be readily stored in air tight moisture proof container and light proof container such as tin cans, covered metal tins, ambered glass containers, wooden boxes and paper bags should not be used for storage of crude drugs.

1.7 Plant Anatomy

Branch of pharmacognosy gives a vital importance to plant anatomical studies. This will help the botanist and pharmacognosy people for the correct identification of herbs. Cell is a main unit of function in a living organism. The cell contains a cell wall and consists of protoplasmic components and non-protoplasmic substances. A group of cells with the identical form and function is known as tissue in which the cell membranes are connected with a pectin layer called middle lamella. The cytoplasmic threads are known as plasmodesmata are considered of cell wall, cell membrane, middle lamella and protoplasm.
They inter-connect the protoplasm of various cells and assist to conduct food, water and communicate stimuli. Plant tissues are divided into three major groups:

- **Dermal Tissues**
- **Fundamental Tissues (Group Tissues)**
- **Vascular Tissues**

### 1.7.1 Dermal Tissues

Dermal tissues consist of outer defensive or protective covering such as epidermis, periderm, trichomes, and stomata.

#### 1.7.1.1 Epidermis

This is the outermost protective single layer of young plant body. The epidermal layer show wide variation in shape. The epidermal cells are narrowly placed with no intercellular spaces. A cuticle layer containing cutin is usually present on the outer surface. The cuticle layer is not epidermal tissue. The structures of the epidermis and stomata are helpful in the identification of leaves.

Straight walled epidermal cells are present in Coca and Senna leaves, wavy walled epidermal cells are found in hyoscyamus, belladonna and stramonium, beaded walls in lobellia and digitalis species, a papillose epidermis in Coca leaves, Suberin, found in the cork cells and cutin, consists of mixtures of polymerized fatty acids such as suberic acid. These compounds give yellow to brown, color with chlor-zinc iodine. Epidermis gives red color with Sudan red and yellow color with potash solution.

#### 1.7.1.2 Periderm (Endodermis)

In periderm lenticels are present which are pores and identical in their function. In lenticels there are no guard cells and they always open. The endodermis is a specialized layer of cells, making the inner layer of the cortex. In mature plants the epidermis is replaced by endodermis due to the activity of the meristematic tissue called phellogen or cork cambium. The cells of the endodermis appear in transverse section four sided, oval or elliptical and often extended in the tangential direction. The cells are longitudinally elongated.
1.7.1.3 Epidermal Trichomes

Trichomes are present on many leaves, herbaceous flowers, stems, seeds and fruits. Trichomes may be differentiated into a base embedded in the epidermal cell and a tube like projecting body. Trichomes are classified into covering and glandular trichomes. **Covering trichomes:** They have protective function. **Glandular trichomes:** They secrete essential oils or oleo-resins. Both glandular and covering trichomes may be unicellular or multicellular, uniseriate or multiseriate and sessile or stalk.

1.7.1.4 Stomata

Stomata are made up of a pair of similar cells called guard cell, placed parallel to each other. It contains a pore in the centre through which gaseous exchange takes place. The epidermal cells surrounding the stomata are called subsidiary cells and they are different in shape. On the basis of arrangement with the subsidiary cells, the stomata are divided into four different types.

**Anomocytic or Ranunculaceous:** This is irregular type stomata. The cells surrounding, the stomata pore are irregularly arranged and it cannot be distinguished from the other epidermal cells, (Examples are lobelia, digitalis,). **Anisocytic or Cruciferous:** Anisocytic stomata are unequal celled type. The stomatal openings or pore is surrounded by three or four subsidiary cells, one of which is markedly smaller than the others, (e.g.; Stramonium, belladonna). **Actinocytic (radiate):** This stoma is surrounded by a circle of radiating cells, (e.g. Ursi).

**Paracytic or Rubiaceous:** Paralled –celled type of stomata. Two subsidiary cells with their long axis are parallel to the pore, e.g. Senna and coca. **Diacytic or Caryophyllaceous:** This is crossed-celled type. The stoma is accompanied by two subsidiary cells with their long axis at right angles to the pore of the stomata, (e.g. peppermint, spearmint, thyme etc).

1.7.2 Ground Tissue or Fundamental Tissues

Fundamental tissue includes cortex, mesophyll, pith, midrib region and hypodermis.

1.7.2.1 Sclrenchyma

Sclerenchyma cells provide mechanical strength to the plant body and are present in all parts of the plant. They occur as stone cells or fibres. These cells are dead and
lignified (cell walls are lined with lignin). The sclereids or stone cells are irregular or isodiametrical in shape. Their walls are transversed by pit canals which are often funnel shaped or branched and usually showing marked stratification. The walls are lignified and thick. Lumen of the cell is small and often the cell contents are of diagnostic significance are present. The pericyclic regions and the bark of woody stems, the hard outer coats of fruits and seeds have the presence of stone cell. They occur in group or insingle.

The sclerenchymatous fibres are usually elongated and narrow with pointed ends. Tissue known as prosenchyma is composed of elongated or spindle shaped cells with pointed ends. The cell walls are usually lignified and composed of pure cellulose. Xylem fibres have smaller pits, tapering ends and thicker walls. They are derived from tracheids. Phloem fibres may be un lignified or lignified. Lobelia and cinnamon bark contains isolated groups of pericyclic fibres.

1.7.2.2 Parenchyma

Parenchyma cells are present in the pith and cortex of stem, mesophyll of leaves and cortex of root. They contain thin walled and living cells with intracellular spaces. Parenchyma cells vary in shape, some contain reticulated thickening and are pitted. Parenchyma with the presence of chloroplasts is known as chlorenchyma and those with large intracellular spaces are called aerenchyma. Photosynthesis and storage are the main function of parenchyma.

1.7.2.3 Collenchyma

Collenchymas are living tissues which are derived from parenchyma cells. The cell walls are thickened due to cellulose deposition hence they have greater mechanical strength. Usually these cells are present in the cortical region of the bark, petiole, and stem and also midrib region of the leaf. The cells are axially elongated and are usually 4 to 6 sided in transverse section.

1.7.3 Vascular Tissues

Transportation of food material and water is the function of vascular tissue system. Xylem (dead tissue) conducts water from roots to leaves. Phloem (living tissue) transports food material from leaves to different parts of the plant.
1.7.3.1 Phloem

Phloem consists of phloem parenchyma, secretory cells, companion cells and sieve-tubes. Sieve plates are areas where vertical series of elongated cells are interconnected by perforation in their walls. Phloem may also have the presence of lactiferous tissue.

1.7.3.2 Xylem

Tracheids, xylem fibres, vessels or tracheae, xylem parenchyma and rays are the structural elements of xylem. Tracheids are elongated tubes with pointed ends. Their cell walls are pitted and lignified. Trachea or vessels comprise of lengthened tubes without any oblique perforated walls. The vessels of protoxylem show coiled or annular thickenings. The later-formed xylem contains reticulate and scalariform thickenings. The thickening of the secondary wall is due to the presence of lignocelluloses. Rays and xylem parenchyma constitute the living meshwork of secondary xylem. The xylem parenchyma is more often than not axially elongated, usually thick and lignified but occasionally thin walled. Presence of concentric zones of xylem parenchyma gives the impression of „false annular rings”.

Vascular bundles may be classified as bicollateral, radial, concentric and collateral, depending on the presence of phloem and xylem. Bicollateral: Vascular bundle is called bicollateral due to the presence of another patch of phloem on the inner side of external phloem. Radial: Here the xylem and phloem occur in distinct patches on varying radii on the axis. Radial vascular bundles are distinguishing feature of roots. Concentric: This is a system where one kind vascular tissue surrounds the other. Collateral: in this system xylem and phloem are arranged side by side in the same radius, with xylem on the inner side and phloem on the outer side. Collateral bundles may be classified as open or close depending on the presence or absence of cambium between xylem and phloem. It is the most frequent kind of vascular bundle found in stem as well as leaves. In monocot stem vascular bundles are scattered whereas in dicot stem bundles are in the form of a ring

1.7.3.3 Cambium

It is a merismatic tissue found in dicot stems present between the xylem and phloem. Though absent in young roots it begins to appear as the plant matures usually between the radically placed xylem and phloem. Later it gives out secondary xylem (on the inner side) and secondary phloem (on the outer side) by forming zig zag rings. In developed
plant part, delicate primary structures are either crushed or poorly represented. Parenchymatous cells constitute the medullary rays which run diagonally from pith of medulla to cortex. Medullary rays run through secondary phloem and secondary xylem.

1.7.3.4 Secretory tissues

Secretory tissues include secretory sacs or cavities, secretory cells, latex tissue and secretory canals or ducts. There is the presence of cells containing oleoresins, oils, resins and mucilage. Lacticiferous tissue (latex) comprises of tubes or cells containing a milky fluid. Vittae of umbelliferae are schizogenous oleoresin canals found in the root stem and leaves. Secretory cells are classified based on their mode of formation.

a) Lysigenous cavity: formed due to dissolution of cells.

b) Schizogenous cavity: formed due to splitting of epithelial cells

c) Schizo-lysigenous cavity: formed by both methods

1.7.3.5 Ergastic cell contents

These are cell contents which can only be identified macroscopically, or with the help of physical and chemical tests. They include proteins, carbohydrates, fats, fixed oils, alkaloids, gums, calcium oxalate etc

1.7.3.6 Starch

Starch from several sources differs in size and shape. Starch occurs in the form of granules in rhizomes, fruits, seeds and roots.

1.7.3.7 Proteins

The ground mass of protein encloses an angular body called crystalloid and one or more rounded bodies. Protein is found in the form of aleurone grains enclosed by thin membrane.

1.7.3.8 Fixed oils and fats

Polysachride complexes formed from sugar and uronic acid units constitute the basic structure of mucilage, gum and pectin. Fixed oil and fats are commonly found in seeds. They either dissolve or swell in water but are insoluble in alcohol. In a cell volatile oils occur as droplets.
1.7.3.9 Calcium oxalate

In plants calcium oxalate occur in five varied forms. Spherical aggregates of sharp pointed angular crystals are called sphaeraphides. Prisms formed from calcium oxalate may occur in small groups or in single. Needle shaped, single or collection of bundles is called raphides. Micro- sphenoidal crystals are found in the cells resembling an amorphous mass. When seen in polarized light these crystals shine brightly.

Silica is found on cell wall as masses (in the interior of cells) and it forms the chemical diatoms. It is soluble exclusively in hydrofluoric acid. Crystoliths it is made of calcium carbonate and are found as small bunches of grapes with stalk made of cellulose. It is known to dissolve with effervescence in hydrochloric, sulphuric and acetic acid.

1.8 Marine Pharmacognosy

Marine Pharmacognosy is branch of Pharmacognosy which deals with marine plant and creatures of ocean. The phrase drug molecule has been appropriately and judiciously employed in line with classic concept, that is a specific chemical entity which essentially posses a marketed pronounced pharmacological activity emphatically on the mammalian organism. In fact, it is the dedicated and concerted efforts of expert researcher from various specialized scientific field that a new drug molecule is isolated, characterized and subsequently subjected to a rigorous preclinical and successful clinical studies and ultimately baptized as a therapeutically effective and potent drug. The marine flora and animal world are rich sources of biologically active compounds.

A large number of sometimes toxic metabolites have been isolated and characterized from protozoan, sponges, coelenterates, echinoderms, mollucs, nemertines, seasnats and fishes. The great interest in these chemically varied compounds has resulted in the development of novel therapeutic agent for the treatment of various disease afflicted by human beings. Marine species studied in recent years have yielded a variety of compounds which possess known or novel pharmacological activities in mammals and have exhibited antimicrobial, antibacterial, and antineoplastic properties. Just as many therapeutically potent drugs have been found in terrestrial plants, it seems likely that a search for new lead molecules from marine organism might uncover unknown entities which could be added to the already existing drug armamentarium.
Isolation, biosynthesis and metabolism of natural products present in marine organisms constitutes an active field of research. One may speculate as to the reasons why there is still relative lack of chemical investigation in the area of marine flora and fauna. It may be due to difficulties in procurement of starting material, isolation and chemical characterization. However this seems unlikely. After all plants for example have presented and still present difficulties. There are many marine biological stations, which already possess and are certainly capable of furnishing large collection of marine species. It is quite uneconomical to extract and purify material of marine species collection, in large quantities from remote corner of the world and therefore the development of drugs from these sources is limited. Newly emerging technologies of cell and tissue culture and genetic engineering may change this situation dramatically by revealing the vast and diverse genetic composition of marine life for pharmacological applications. Marine micro-organisms isolated from marine environment and cultivated under conditions pertinent to sea water for antibiotics and enzyme production can be of great help in this direction.

Several well known products of marine origin have been in use for many years. Agar, alginic acid, cold liver oil, halibut liver oil, spermaceti, protamine sulphate, carrageenan etc. have been studied in detail since many years and their medicinal, economical and commercial values are well established since a long time. Although the use of marine organisms in folk medicine is quite restricted since last four to five decades but many of these substances have demonstrated interesting biological activities. This topic has been devoted to marine natural products derived from marine organisms with an emphasis on the metabolites that possess the prominent biological activities.

Marine toxins were reported to possess an extremely high potency with regard to their pharmacological actions, and therefore, sometimes collectively referred to as „toxins“. The doctrine and philosophy of Paracelsus advocating that the clinical efficacy and usefulness of an active principle is nothing but a matter of the right dose administered by the right route”- carries a lot of value and impact. Nevertheless, the joint efforts by phytochemists and medical scientists may pave the way to assess the plethora of the currently labeled „marine toxins“ for their usefulness as drugs and or as physiological tools that may ultimately decode the mechanisms responsible for cellular processes solely.
characteristic of life but unfortunately not revealed till date. It is indeed a very critical as well as a crucial turning point when phytochemistry, medicinal chemist and pharmacologist will put their knowledge, wisdom, expertise, skill and resources together to unravel the wealth of drugs beneath the sea as they already have accomplished toward the terrestrial plants almost a century ago; and towards soil, samples nearly half a century ago for antibiotic (when penicillin was discovered by Alexander Fleming).

Marine pharmacognosy is exclusively focuses upon a good complication of certain vital and important 'marine biological,' having established chemical structure and proven pharmacological activities. So far, more than five lakh species of marine organism have been well-documented from the ocean across the globe. Interestingly, quite a sizeable number of such marine organisms do possess a wild-spectrum of biological activities, namely: anti-biotic, anti-viral, ant-neoplastic, cytotoxic, ant-imicrobial, ant-inflammatory, enzyme inhibitors, prostaglandin, neuro-physiological and cardiovascular agents.

1.8.1 Classification of Drug Molecules of Marine Organism

1.8.1.1 Cytotoxic/Antineoplastic Agent

The prominent US-based research institutes, namely; Unites States: National Cancer Institute (NCI) and US: National Sea Grant Office (NSGO) have discovered thousand of pure and semi pure compounds derived from the marine origin that distinctly exhibited antineoplastic/cytotoxic activities in a good number of cell lines; beside in vivo action against both malignant tumor and leukemia in various animal models (Vinod 2003).

a. Cambranes
b. Macrolides
c. Dipipeptides
d. Miscellaneous compounds

Cambranes

Cambranoids are the 14 membered cyclic diterpenes obtained from a wide variety of soft corals. A good number of cambranoids have been isolated and characterised. Most of these compounds contain an exocyclic lactone as their integral part. These compounds are discussed individually in following Table 3
Table 3. Examples of Compounds Cambranes

<table>
<thead>
<tr>
<th>Name</th>
<th>Biological Source</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinularin</td>
<td>Dihydro congeners obtain from Sinularia flexiblis</td>
<td>Anti cancer activities</td>
</tr>
<tr>
<td>Crassin acetate</td>
<td>From caribbean gorgonian Pseudo plaxaura porosa</td>
<td>Human leukemia, mouse fibroblasts</td>
</tr>
<tr>
<td>Aplysistatin</td>
<td>Obtained from aplysia angasi</td>
<td>Antineoplastic agent</td>
</tr>
<tr>
<td>Non-lactonic cembranoid:</td>
<td>Obtained from chloroform extract of aplidium species</td>
<td>Cytotoxic to leukemia and mammary carcinoma, radioprotective agent</td>
</tr>
<tr>
<td>Geranylhydroquinone</td>
<td>Obtained from the gorgonian coral</td>
<td>Exhibits cytotoxic activities</td>
</tr>
</tbody>
</table>

1.8.1.2 Cardiovascular Active Drugs

During the past three decades a huge number of extract; fraction and pure isolates from thousand of marine organism were subjected to thorough cardiovascular screening in various research laboratories around the world. The cardiovascular active drugs may be broadly classified as:

Cardiotonics

The cardiotonic compounds showing positive response in either in vivo/in vitro intropic activities on whole or parts of the heart these are classified and which is shown in Table 4.
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Biological Source</th>
<th>Features</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laminin</td>
<td>Obtain from marine algae Laminaria angustata</td>
<td>Abundant structural compound</td>
<td>Shows hypotensive effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Critical to the stability of the extracellular matrix and to adhesion of cell</td>
<td>Exhibit diverse biological activities</td>
</tr>
<tr>
<td>Octopamine</td>
<td>Obtain from salivary gland of octopus vulgaris, octopus macropus and eledone moschat</td>
<td>Obtained as crystal from hot water that get changed at about 160°C to a compound which melts above 250°C (decompose)</td>
<td>Cardiovascular adrenergic response in anaesthetized dog and cats</td>
</tr>
<tr>
<td>Saxitoxin</td>
<td>Produced by the dinoflagellates gonyaulax catenella and G. tamarensis</td>
<td>White hygroscopic solid, pKa in water, extremely soluble in water, methanol, sparingly soluble in ethanol, glacial acetic acid</td>
<td>Exhibit hypotensive effect, employed as a tool in the neurochemical research.</td>
</tr>
<tr>
<td>Autonomium chloride</td>
<td>Found in Verongia fistularis</td>
<td>Posses isosetric structure of adrenaline and acetyl choline</td>
<td>CNS stimulant, cardiotonic</td>
</tr>
</tbody>
</table>
1.8.1.3 Hypotensive compounds

There are quite a few potent hypotensive compounds that have been derived from a variety of marine organism these new ranges of medicinally active chemicals are classified as follows which are shown in Table 5.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Biological Source</th>
<th>Features</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doridosine</td>
<td>Obtained from nudi branch Anisodoris nobilis</td>
<td>Revealed on the basis of the kinetics of the enzymatic degradation of these nucleosides</td>
<td>Most potent hypotensive marine nucleoside, exert hypothermic effect</td>
</tr>
<tr>
<td>Hypotensive peptides</td>
<td>Obtained from Aaptos aaptos</td>
<td>Heterocyclic nucleus its structural characteristic and paratical size which may render this molecules a good candidate for the drug.</td>
<td>Has adrenergic blocking effect, causes hypotensive effect</td>
</tr>
<tr>
<td>Aaptamine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.8.1.4 Marine Toxins

A host of marine bio-toxins have been obtained from wide variety of marine organism in their crude, semi pure form. However during the eighties a good number of them possessing venomous and toxic properties and having most complex chemical structures have been isolated, characterized with the advent of rather exceedingly sophisticated analytical instrument and concerted effort of dedicated marine chemists and pharmacologists across the globe. Examples of marine toxins are shown in Table 6.
### Table 6. Examples of Marine Toxins

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Biological Source</th>
<th>Features</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palytoxin</td>
<td>Obtain from zanathid coral of the genus Polythoa</td>
<td>White amorphous hygroscopic solid powder, does not have specific mp get charged when heated</td>
<td>Potent coronary vasoconstrictor, used as anti-anginal, chemotherapeutic agent</td>
</tr>
<tr>
<td>Tetrodotoxin</td>
<td>Obtain from ovaries and liver of species of tetraodontidae</td>
<td>Slightly soluble in water, absolute in ethanol ether has dissociation constant pKa=8.76(water)</td>
<td>Employed as valuable pharmacological tool</td>
</tr>
<tr>
<td>Brevetoxin</td>
<td>Obtain from the dinoflagellate Ptychodiscus brevis</td>
<td>Lipid soluble toxins, do not contain N atom</td>
<td>Causes neurological and gastrointestinal disorders, used as cardiotonic in laboratory animal heart studies</td>
</tr>
<tr>
<td>Ciguatera toxins</td>
<td>Obtain from Gymnothorax javanicus</td>
<td>Natural polyether structural chemical substance, less toxic analogue</td>
<td>Causes neurological, cardiovascular an gastro-intestinal problems</td>
</tr>
</tbody>
</table>
1.8.1.5 Antimicrobial Drugs

A plethora of important antimicrobial drug substances have been isolated, characterized and studied extensively over the past three decades particularly from the vast domain of marine organism which are shown in Table 7

Table 7. Examples of Antimicrobial Drugs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Biological Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zonarol</td>
<td>Obtained from Dictyopteris zonaroides (brown algae)</td>
</tr>
<tr>
<td>Prepacifenol</td>
<td>Obtained from laurencia pacifica and Laurencia filformis (red algae)</td>
</tr>
<tr>
<td>Polyhalo-3-butene-2-one</td>
<td>All four isomers of this are obtained from Asparogopsis taxiformis</td>
</tr>
<tr>
<td>Tetrabromo-2-heptanone</td>
<td>Obtain from another species of red algaees Bonnemaisonia hemifera</td>
</tr>
<tr>
<td>2-cyano-4,5 -dibromopyrrole</td>
<td>Obtain from Agelas oroides, a special type sponge found in marine species</td>
</tr>
<tr>
<td>Aeroplysinin-1(+) and aeroplysinin-1(-)</td>
<td>Two isomers obtain from Verongia aerophoba another species of sponge</td>
</tr>
<tr>
<td>Eunicin</td>
<td>Obtained from Eunicia mammosa the well known Gorgonian corals</td>
</tr>
</tbody>
</table>

1.8.1.6 Antibiotics Substances

Interestingly between a span of almost twenty years thousands of marine based extract, fraction and pure isolates were evaluated for their antibiotic activity. However, the rate was not only miserable but absolutely non-significant. As on date, not even a single marine derived antibiotic substance has been able to either supersede or gain enormous recognition with regard to their board spectrum of activity and superb quality of the known
and available antibiotics obtained from the innumerable terrestrial organisms, semi-synthetic products and for purely synthetic ones and examples where described in Table 8.

**Table 8. Examples of Antibiotics Substances**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Biological Source</th>
<th>Features</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okadic acid</td>
<td>Obtained from Halichondria (marine black sponges)</td>
<td>Obtain from dichloromethane / hexane crystal in form</td>
<td>Tumor promoter, cytotoxic to KB cells, able to transport divalent cations</td>
</tr>
<tr>
<td>Acanthifolicin</td>
<td>Obtained from Pandaros acanthifolium</td>
<td>Posses antibacterial activity cytotoxic action, found lethal to mice</td>
<td>Same as okadiacid</td>
</tr>
<tr>
<td>Norhalichondrin</td>
<td>Obtained from Halichondria okadai (sponge)</td>
<td>Polyether macrolide</td>
<td>Found to exert antitumour activity</td>
</tr>
</tbody>
</table>

1.8.1.7 Anti Inflammatory and Antispasmodic Agents

A plethora of chemical substance has been isolated from the board spectrum of marine organism which attribute either anti-inflammatory or anti spasmodic activities and examples where shown in Table 9.
Table 9. Examples of Anti Inflammatory and Antispasmodic Agents

<table>
<thead>
<tr>
<th>SI. No</th>
<th>Chemical Name</th>
<th>Marine Organism</th>
<th>Common Name</th>
<th>Biological Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dendalone-3-hydroxybutyrate</td>
<td>Phyllospongia</td>
<td>Sponge</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>2</td>
<td>Flustramine A and B</td>
<td>Flustra foliaceae</td>
<td>Swedish marine moss</td>
<td>Antispasmodic</td>
</tr>
<tr>
<td>3</td>
<td>Tetradotoxin</td>
<td>Spheroids rubripes</td>
<td>Globe fish</td>
<td>Strong anti-spasmodic</td>
</tr>
<tr>
<td>4</td>
<td>6-n-tridecyl salicylic acid</td>
<td>Caulocystis cephalornithos</td>
<td>Brown algae</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>5</td>
<td>Flexibilide</td>
<td>Sinularia flexibilis</td>
<td>Soft coral sponge</td>
<td>Anti-inflammatory</td>
</tr>
</tbody>
</table>

1.8.2 Marine Natural Products: An Up Gradation Profile

In the last two decades an overwhelming thrust in the research towards the accomplishment of an up-gradation profile of marine natural products have taken place. However, this achievement could only be possible either through various microbial transformation or by means of semi-synthetic structure analogues of puupephenone. Interestingly marine natural products were subjected to rigorous bioconversion studies and different specific organia reactions such as acetylation, addition of halogen acid, Grignardization, conjugate additions, and other addition reaction.

In short the marine world evidently and explicitly enjoys the status of holding an enormous or tremendous potential towards the epoch making discovery of an altogether new lead compounds in the development of medicinally therapeutic agent that are active against a variety of parasitic infection and ailments. The wide range of vat sources tapped from the marine fauna and flora that would certainly help in the evolution of the previous known chemotype for stemming the influx of crucial drug resistant microorganism and insects. In order to explore, tap and above all exploit commercially the relatively virgin
biological reserves exclusively depends on the use of rapid technological advancement towards their collection, preservation, identification and characterization of trace quantum of essential secondary metabolites.

1.9 Indigenous Traditional Drugs

Medicinal plants have been playing a significant role in the treatment of various ailments in India. The important traditional methods in our country are Ayurveda, Homeopathy, Unani and Sidha systems of medicine. Ayurveda offers traditionally a highly scientific health-care therapy as a divine gift, and as a result, the global interest of the medical profession is nucleated on the Ayurvedic and Unanic systems of medicine. A traditional ingredient, is fundamentally preventive, protective, nutritive and curative. Therefore, traditional medicines are safe, sure and harmless which treat the patients and does not end at rendering relief.

In spite of phenomenal progress in the area of development of new drugs from synthetic sources and appearance of antibiotics as major therapeutic agents, plants continue to provide basic raw material for some of the most important drugs. An analysis of prescriptions dispensed from community pharmacies in USA was carried out in 1973, and this showed that as many as 41% prescriptions contained one or more products of natural origin as the therapeutic agent of these prescriptions, 25% were based on drugs from higher plants, some 13% represented metabolites of microbes and about 7% were of animal origin (Mohammed 1998).

Among 200 of the most frequently prescribed drugs in USA, 25% were of natural origin. The situation would appear to be similar for many other countries including India, Russia, Germany, England, Italy, China and Japan. About three hundred herbal drugs of Indian origin are used in England to treat various diseases. The Pharmacopoeia of the Peoples Republic of China, issued in 1978, describes 882 crude drugs of which 637 are of plant of origin, Japanese Pharmacopoeia released in 1981, contained 102 plant drugs.

1.10 Scope of Pharmacognosy and Phytochemical Industry in India

Since arbitrary use of synthetic drugs and antibiotics has resulted into serious symptoms all over the world, grasp for herb based raw materials for pharmaceuticals has improved extremely. Moreover, the synthetic drugs and intermediately chemicals are
extremely expensive. Further, more approximate one third of all drugs are plant-based and if bacteria and fungi are also built-in, nearly sixty per cent of pharmaceuticals are of herbal source. Our country has the richest source of chemical constituents in the formulation of drugs for curing dreaded disorders.

A drastic come-back of herbs and nowadays there is a new starting of herbal era in the entire world. Today herbal products symbolize safety and synthetic products are considered unsafe both for human being and enviroment. Herbs had been worth for its flavor, medicinal and fragrant character for centuries. The artificial or synthetic goods of the current period exceeded its importance for a short time. However the people of the new era are returning to nature because of security and safety at oftens. For health care three –quarter of the global community depends on the medicinal extracts from plants.

At one time or other time about 35 % of the whole plant species are used for its medicinal property. About two crore rupees are estimated in the world-market for the drugs which are derived from plant kingdom. In fast developing countries like India and China are contributing 80% of the herbal drugs to global market. The financial significance of medicinal-plants is much supplementary to nation like India than to unwind of the globe. India provides two third of the flora employed in current scheme of the medicine and health-care scheme of the rural inhabitants depends on the native systems of the medicine (Kumar et al 2014).

India is known as the 12th Biodiversity Center due the occurrence of 45,000 various herbal species. The biodiversity is unmatched owing to the presence of 426 biomes or habitats of specific species, 16 different Agro climatic sectors, 25 biotic zones. Among these herbs, about 15,000-20,000 flora have high-quality therapeutic value. Since, drugs of herbal resource have been used in customary system of medicines like Ayurveda, Unani and Siddha. In India, the alternative systems of medicine like Ayurveda, Unani and Siddha use about 600-700 species of curative plants and modern medicine uses around 30 species of plants. The plant drugs are obtained from different organs like stem, root, bark, seeds, leaves and also from whole plant. Some drugs are obtained from latex and gum-resins. In modern pharmacopoeia a number of plant derived drugs are adopted as medicine even in the allopathic system, which outline an important segment in the modern medicine.
The herb collectors and small traders collect the drugs for the manufactures of Ayurvedic and Unani drugs. But there is a shortage of these materials for maintaining the sustained supply to the plant based drug industries. It is also not proper under the present situation to be dependent only on natural resources to keep the wheel of the industries running all the time in view of the fast depleting natural wealth. At the same time increased demand of herb raw materials, has led to over exploitation of wild plants resulting into serious hazard. This necessitates the urgent need of their systematic cultivation for constant supply to the user industries. Domestication and cultivation of some of the vital plants are essential to deal with constant demand of stable contribute for the phytochemical industries.

One of the new areas in medicinal development during the recent years has been the use of adaptogenic drugs from plants. Most of these drugs are used as general tonic and stimulants to improve the defense mechanism of the body and protect the body against stress and infections. These drugs also help the body to improve and tone up metabolism in old age and in persons weakened by serious diseases. In spite of the incredible progress in medicine there is a number of diseases for which recent medicine has veto cure. In such cases it treats only symptoms to provide relief to the patients.

These included vital diseases such as herpes, muscular dystrophy, Parkinsonism, alcoholism, smoking, obesity, genetic disorders, arthritic diseases, liver disorders, HIV and cancer etc. Recent trends have shown that plant drugs have answer to such cases. In recent times a number of formulations based on Ayurvedic medicine have come to the market to control liver diseases and some of these have been found successful in these diseases. There is a sizeable capacity to display such plants for active constituents” which may be used in future for treatment of such incurable disorders.

Higher plants, microbes and animals are the main sources of crude drugs. However, enzymes and antibiotics used in modern medicine are obtained from animals and microbes. For the study of herbs, they may be classified according to morphological, taxonomical, chemical constituents and pharmacological activities. Morphological classification is more helpful to identity and detects adulteration. For studying evolutionary developments, the drugs are classified according to taxonomical classification. The activity of drug is due to its chemical constituents and therefore the drugs are divided according to the
presences of chemical components. The pharmacological classification of herbs is more relevant to study therapeutic utility of the plans.

1.11 Future of Herbal Drugs

Foliages are still a persuasive resource of remedial agents. They are colonized due to their value, trouble-free accessibility, stumpy cost and somewhat being devoid of grim venomous effects. Some herbal drugs (like *Achyranthes aspera* used as diuretic, *Acorus calamus* as tranquillizer, *Artemisia vulgaris* (cardiotonic), and *Butea frondosa* is used as antihelmintic, etc) have been proven to exhibit the respective pharmacological activities. A derivative of artemisinin prepared from *Atemisia annua* is effectual against opposed to strains of *Plasmodium falciparum* where synthetic anti-malarial fails to remedy the different diseases.

A flavonoid separated from *Silybum marianum* has been approved as drug against different liver disorders in western countries. Iriodoid glycosides called valepotriates obtained from Valeriana sp have been used as tranquillizer and sedative in European countries. Total saponins from the Indian plant *Commiphora mukul* often referred as guggulipid have been approved as hypolipidemic agent for lowering blood cholesterol. A derivative of podophyllotoxin obtained from *Taxus species* have been approved as anticancer agent.

1.12 Antioxidants

Normally for the stability of any atomic orbital, a presence of at least 2 electrons, spinning in opposite direction, is necessary as is seen with most biological molecules which are termed as non-radicals (meaning non-free radicals). A free radical is a molecular species having an unpaired electron and thus is a highly reactive entity (being unstable). Free radicals are formed constantly in human system either as accidental products during metabolism or deliberately during the process of phagocytosis. Apart from these, free radicals can also be generated from toxic environmental pollutants, ionizing radiations, ozone, heavy metal poisoning, cigarette smoking and chronic alcohol intake etc Free radicals thus formed, being highly reactive, can oxidize biomolecule leading to tissue injury and cell death.
To stabilize itself, a free radical may donate its unpaired electron or may accept one from other biomolecule transforming a non-radical to another free radical to set up a disastrous chain reaction. These free radicals are normally scavenged removed) by several enzymatic and non-enzymatic antioxidants defense mechanisms (see below). If these defense mechanisms are inadequate, a situation called “oxidative stress” occurs which leads to lipid per-oxidation, protein and DNA damage causing tissue injury and cell death. However, if 2 free radicals combine, the 2 unpaired electrons are shared by each other to form a covalent bond. Their reactivity is thus terminated.

1.12.1 Antioxidant Activity

A free radical measured, as fragments of molecules, are very reactive in the environment, recognized as reactive oxygen species (ROS) short lived and continuously produced during the normal functions of the body. Mainly these radicals are generated though smoke, ecological pollutions, vehicle fumes, cigarette, radiation and air pollutants. Obviously, here ther is a lively equilibrium among the sum of free radicals generated and antioxidants to guard the body against their harmful consequence.

The free radicals can be trapped directly by phenol compounds though a coupled reactions with antioxidant enzymes (Reynolds et al 1999). Presently accessible synthetic antioxidants like butylated hydroxytoluene, butylated hydroxyanisole and tertiary butylhydroquinone are supposed to cause pessimistic wellbeing effects. Hence, there is a tendency to swap synthetic antioxidants with natural antioxidants. In addition, these synthetic antioxidants show short solubility and reasonable antioxidant activity (Pourmorad, 2006). Free radicals are electrically charged and have an unpaired electron to incarcerate electrons from supplementary substances to deactivate by them.

1.12.2 Free radical Formation

A free radical is produced, whilst covalent bonds amid the entity are busted and one-electron is left over with recently created atom and these are extremely imprudent due to the existence of unpaired electron (Karlsson, 1997). Free radicals include two unpaired electrons and a fresh free radicalis formed when it takes an electron from flanking compound or molecule and shown in Fig 1 (Goldfar, 1999).
This writing suggests that, everywhere 2-5 percentage of the entire oxygen intake have the capacity to injurious superoxide radical via electron break out during both rest and exercise (Sjodin et al 1990). In circle, electron getaway from the ETC is augmented and when premeditated, six to four ml/kg/min to 4 mill/kgm/minute of the in general O$_2$ intake for the period put into effect, have knack to produce the free radicals (Dekkers et al 1996).

1.12.3 Measurement of Free radical

Multiple methods for free radicals measurement are available, with their own merits and demerits. Aldehydes are generally considered as a general indication of free radical production such as TBARS (Clarkson 1995). Due to the lack of specificity, reproducibility and sensitivity the Thiobarbituric Acid (TBA) test is a challenge. So the LC (liquid chromatography) is used in its place of spectrophotometer techniques help to reduce the errors (Halliwell et al 1993).

1.12.4 Mechanism of Antioxidant Defenses

The antioxidants work to shield lipids from the per-oxidation by the radicals (Kishore 2010). The antioxidants are the molecules having the capacity to slow down or put off the oxidation of another molecule. It has proved that, a diet rich in antioxidant helps to prevent the coronary artery disease (CAD) (Miller 2004). The best source of antioxidants is colored fruits and vegetables (Erin DRD 2006). Some more examples of antioxidants are mentioned in Table 10.
### 1.12.5 Requirement

The utilization of oxygen increases during exercise that may lead to increase in the production of free radical and body counters it through the antioxidant defense system (Alessio et al 1997). Free radicals shaped at some stage in unrelieved form, when put into effect may beat the defensive ability and antioxidant-defense system of the body. Thus assemble the body-immune to ailment or harm. Consequently, the free radical supply is needed in the antioxidant defense mechanism.

### 1.12.6 Reactive Oxygen Species

Free radicals can be negatively charged, positively charged or electrically neutral. The later includes inorganic species like hydrogen peroxide (H$_2$O$_2$), hypocholorous acid (HOCl) and nascent singlet oxygen (O.H$_2$O$_2$) and HOCl are not free radicals but are very powerful oxidizing agents. Nascent oxygen is a transient atomic state of oxygen which is

---

**Table 10. Example of Antioxidants**

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Non enzymatic antioxidant</th>
<th>Antioxidant sequestering ion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lipid soluble</td>
<td>Water soluble</td>
</tr>
<tr>
<td>Cytochrome oxidase System</td>
<td>α-tocopherol (Vit.E)</td>
<td>Albumin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ascorbic acid</td>
</tr>
<tr>
<td>Super oxide dimutase</td>
<td>β-carotene (Vit.A)</td>
<td>Bilirubin Ceruloplasmin</td>
</tr>
<tr>
<td>Catalase</td>
<td></td>
<td>Cysteine</td>
</tr>
<tr>
<td>Glutathione peroxidase</td>
<td></td>
<td>Gluthathione</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uric acid</td>
</tr>
</tbody>
</table>
highly reactive than O\textsubscript{2} and is implicated in the causation of several oxidative processes and photosensitization reaction. Such highly reactive species which are not free radicals in true are called reactive oxygen species (ROS).

1.12.7 Promoters of Free Radicals

Several transition metals (example iron and copper) have variable oxidation numbers which accordingly can accept a single electron from or donate it to non radicals. As a result these metals serve as excellent promoters of free radicals. For example, iron and copper ions can convert H\textsubscript{2}O\textsubscript{2} into highly reactive free hydroxyl radical (OH). This can accelerate lipid per-oxidation and lead to the accumulation of highly cytotoxic end products.

1.12.8 Antioxidants and Clinical Uses

Antioxidants therefore can intervene at any of the following, between the processes of free radicals generation to the causation of tissue injury:

1. Blockage of the generation of toxic free radical,
2. Blockage of the chain reaction set by free radical
3. Scavenging of free radical
4. Blocking the secondary generation of toxic metabolite or mediator
5. Enhancing antioxidant capability

Thus antioxidant radicals scavengers which at low concentration can prevent or delay the oxidation of lipids, carbohydrates, proteins and nucleic acids to improve the quality of life by retarding the aging process. To prevent free radical formation and eventual tissue damage, our body has an array of antioxidant defense system, which allows us to cope with the "oxidative stresses "inflicted by free radicals.

1.12.9 Classification of Antioxidants

Antioxidants are mainly classified as endogenous and exogenous types. The classifications of antioxidants with examples are given in Table 11.
Table 11. Classification of Antioxidants of Clinical Uses

<table>
<thead>
<tr>
<th>SI. No</th>
<th>Antioxidants</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Endogenous antioxidants</td>
<td>Superoxide dismustase SOD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glutathione reduced form</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carotenoids (beta carotene)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melatonin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alpha tocopherol (Vitamin E)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ascorbic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Adenosine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lactoferrin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nicotinamide</td>
</tr>
<tr>
<td>2</td>
<td>Exogenous antioxidants</td>
<td>Xanthine oxidase inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trace elements and minerals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antioxidants from plant sources</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spirulina</td>
</tr>
</tbody>
</table>

1.12.9.1 Endogenous antioxidants

1.12.9.1.1 Superoxide dismustase (SOD)

These enzymes found in all cells, scavenges superoxide ion and prevents its accumulation so that cells are protected from oxidative stress. SOD catalyses dismutation reaction in which one $O_2^-$ is oxidized to $O_2$ while the other is reduced to $H_2O_2$. SOD can afford protection against gastrointestinal ischemia, ischemic reperfusion pancreatitis, myocardial infarction, injury, organ transplant and endotoxic shock.

Oxygen molecule deficient of one electron is also called super oxide ion. These are derived from inevitable leakage from the mitochondrial electron transport chain reaction. These are also generated during metabolism of various drugs by cytochrome P-450.
microsomal oxidative system, (example paracetamol or alcohol). Some enzyme also catalyse the formation of these free radicals, example during oxidation of hypoxanthine to xanthine and to uric acid superoxide (O$_2^-$) ions and hydrogen peroxide are formed.

1.12.9.1.2 Glutathione Reduced Form (G-SH)

Glutathione peroxidase scavenges toxic amounts of the peroxides and free radicals and also reduces the formation of low density lipid (LDL). Glutathione is an excellent cytoprotective and very good antioxidant. It prevents free radicals induced oxidation of SH groups of various protein to disulfide derivatives. G-SH improves the outcome of organ transplant, reperfusion, cystic fibrosis and disease in HIV positive patients.

1.12.9.1.3 Beta Carotene

It is Vitamin A precursor, which also serves as an antioxidant and reduces the risk of cancers due to free radical damage. It has also been known to provide protection from heart attack and photo-sensitization because of its antioxidant properties.

1.12.9.1.4 Melatonin and Alpha-tocopherol (Vit E)

It catalyses the action of various enzymes involved in the activity of endogenous antioxidants. Being antioxidant, supplements of Vitamin E provides protection against neurological damage, atherosclerosis, thrombotic vascular diseases and retrolental fibroplasias. Increased intake of Vit E compensates for selenium deficiency-induced adverse effects of free radicals.

1.12.9.1.5 Ascorbic Acid

Deficiency of ascorbic acid predisposes to atherosclerosis and carcinogenicity. Ascorbic acid reacts with H$_2$O$_2$, peroxide and superoxide free radicals and itself oxidized to dehydroascorbate in this process. Smokers have defective antioxidant protection. Both Vitamin C and Vitamin E inhibit nitrosamine formation.

1.12.9.1.2. Miscellaneous antioxidants

1.12.9.1.2.1 Adenosine

It is an endogenous anti-inflammatory antioxidant that offers protection against reperfusion injury. Adenosine inhibits superoxide generation by NADPH oxidase in neutrophils and macrophages.
1.12.9.1.2.2 Lactoferrin and Nicotinamide

It is circulating iron binding protein that reduces iron-dependent free radical toxicity and affords protection against lung cancer. This is used to protect against tissue injury due to oxidative stress.

1.12.9.2 Exogenous Antioxidants

1.12.9.2.1 Xanthine Oxidase Inhibitors

This antioxidant promotes super-oxidation during reperfusion injury, myocardial infarction, cerebral and gastrointestinal re-oxygenation injury.

1.12.9.2.2 Trace Elements and Minerals

Selenium is a trace element which enhances the antioxidant activity of Vit E. It is also promotes synthesis of glutathione per-oxidize as well as stimulates the immune system of the body and therefore, is a most favored ingredient in various, antioxidant formulation. Manganese, zinc, copper and chromium are the source for generating superoxide dismustase, glutathione per-oxidize and catalyze the enzymes. (Sharma 2008)

1.12.10 Other Free Radicals

Other important free radicals are hydroxyl (OH), proxy (RO.) and nitric oxide free radical (NO.) All these free radicals induce oxidative destruction of polyunsaturated fatty acids (PUFAs) of cell membranes (lipid per oxidation). This directly disrupts the integrity and function of biological cell membranes and even destabilizes membrane receptors. The cellular components also suffer damage due to reactive aldehyde production. Attacks on proteins inactivate enzymes while damage to nucleic acids causes breaks in DNA strands. Free radicals are regarded as carcinogenic because of the damage they inflict on DNA.

1.12.11 Importance of Free radicals

The resistant scheme is the body system that utilizes free radicals. Overseas invaders are noticeable by means of free radicals by the impervious arrangement. It will permit resolving for in which, the tissue is require to be aloof commencing from the body. However, free radicals are obviously bent by some systems within the body and have useful effect that cannot be over looked. Oxidation, protein and DNA damage causes tissue injury and cell death. However, if 2 free radicals combine, the 2 unpaired electrons are shared by each other to form a covalent bond. Their reactivity is thus terminated.
1.12.12 Antioxidant from Herbal Sources

Grape fruit juice, garlic, turmeric (containing curcumoids), tomato (which contain carotenoid which is a red color pigment) and herbal preparations containing bioflavonoid also possess good antioxidant properties. These are considered much safer in day to day use. These are claimed to reduce the risk of myocardial infarction, atherosclerosis and different cancers. Spirulina is blue green algae from shallow pond water having excellent antioxidant properties. It is a good source for superoxide dismustase, beta carotene and B-complex vitamin. It is used singly or combination which other vitamin and minerals in various antioxidant preparations.

1.13 Wound healing

Wound is cut, burn, puncture, discontinuity or break in the surface of the epithelium (Alison 1992). World”s 8% of the inhabitant relies on medicinal herbs for their chief healthcare, and World Health Organization (WHO) promoting customary medication as a cause of medical care, above all in upward countries (Farooqi 2001, Sanjay 2007). In India cure of the disease is based on the treatment with herbal drug in ancient times. Different medicinal plants have many uses like snakebite inflammation, leprosy etc (Mukherjee et al 1997). Plants will repair the mechanism very effectively and early. Fig 2 represents the wound healing process.
1.13.1 Types of Wounds

Depending on the mode in which the skin or tissue is broken down, the wounds are classified into the following way.

- **Incision**: Incisions are generally called as cuts and they are caused by any pointed device or broken glass. When incisions are at skin surface bleeding will be more.
- **Puncture**: Objects (nails, needles, wire and bullets) that rupture into the tissues while leaving a small opening.
- **Abrasion**: Skin being scraped along a hard surface and abrasions are repaired when the skin is worn out.
- **Contusion/Bruise**: It is usually created by the blunt blow. In this case tissues and blood vessels will lying underneath will get damaged. This will cause a discoloration the surface of the skin by the bleeding from the minute vessels.
- **Strains**: These are caused by the injuries to the muscles or to tendons by stretch and stiffness followed by the swelling.
• **Sprains**: are damage in the nearby joints and it usually happens because of excessive movement of the joint.

• **Amputations and Cavity**: Amputations are injury to the body parts by the non-surgical removal of the particular parts.

• **Avulsion and Laceration**: These are ragged unshared edges and masses of the underline tissues.

1.13.2 General Procedure for Wound Healing

The repair of wound involves mainly two distinct processes that are; regeneration of the injured tissues by parenchymal cell and contraction of wound and replacement of connective tissue. The healing wound is a dynamic and changing process, which consists of inflammatory phase of 0-5 days, which begins at the very time of injury followed by fibroplasias (3-14 days), which is followed by tissue remodeling (up to 1 year) and scar formation, which is the final product of healing process. Skin ulcers which is very common is diabetic patients Fig 3 represents the skin ulcer-wound starting and till the ending process.
1.13.3 Management of Wound

Management of wound is one of the major problems in the world and wound can be caused due to chemical, biological or physical agents. Wound can be classified based on their etiology, morphology and lasting period characters etc. Color code concept was used.
where wounds were classified as red, yellow or black. Based on the nature and depth wounds can be classified as closed and opened. Depending on the concentration of the wound, they can be termed as; simple or compound wound. In simple wound, the damage is only to the skin and in case of complex wound; the wound involves the underlying tissues, tendons etc (Naira 2010). Fig 4 shows the renovation of connection following the wounding.

![Renovation of Connection Following Wounding](image)

**Fig 4. Renovation of Connection Following Wounding**

a. Normal skin, b. Incision, c.Fibroblasts, d. Scar
1.13.4 Healing of Wound

1.13.4.1 Primary Intention

These types of wound healing is seen when the wound is a clean incised wound. The several overlapping stages in the repair process of primary infections are **Inflammation:** The cut surfaces become inflamed and the gap will be filled by the clot and debris. **Proliferation:** It is the proliferation of upper part of the skin around the cutted area and clot is formed. **Maturation:** In this, the granulation tissue is replaced by fibrous scar tissue. Rearrangement of collagen fibres occurs and the potency of the wound increases and becomes less vascular. Three phases of wound healing are shown in Fig 5.

![Inflammation Proliferation Remodeling]

**Fig 5. Three Phases of Wound Healing**

1.13.4.2 Secondary Intention

When the wound edges are separate, there is tissue loss and sometimes the wound may be infected. Rapid closure of the wound is not possible and this may leads to an ugly scar and sometimes may cause limitation of movement. The different stages of recovery process of secondary infections are; **Inflammation:** Develops on the surface of the healthy tissue and separation of necrotic tissue begins, due to the action of phagocytes in the inflammatory exudates. **Proliferation:** begins as granulation tissue, consisting of capillary buds, phagocytes and fibroblasts, develop at several months, waiting till the complete thinness of the skin is restored. The fibrous scar tissue is shiny and does not contain sweat glands, hair follicles or sebaceous glands (*Anne 2001*).
1.13.5 Skin Wound Healing

Wound healing of the skin begins from the bottom and spreads to edges. The collagen structure is in the collagen formation is in position, the going upcomplex of blood vessel migrate to it. The healing of big wounds can be complex by many factors. Contracture is a process of wound healing and any infections can also deter the wound healing.

1.13.6 Epidermal Wound Healing

The exposed location of skin makes it vulnerable to trauma because of physical and chemical stimuli or stresses. These cells then enlarge and migrate across the wound. The cells appear to migrate as a sheet until advancing sheets from opposite sides of the wound meet. When the epidermal sheets encounter each other, their continued migration will stop by contact inhibition. Continued migration of the epidermal cell stops when it is finally in contact on all sides with other epidermal cells. Thus, they have the ability to invade body tissues with few restrictions. The events involved in epidermal wound healing occur within 24 - 48 h after wounding.

1.13.7 Deep Wound Healing

When a wound spreads to the tissues and to the epidermis the wound healing process becomes more complex and it results in the formation of scars. The first and second steps of wound healing involve inflammation and clot formation respectively. The third phase i.e proliferative is resolute by the extra development of epithelial tissues under the scab and it may cause the deposition of fibers in irregular shape. In final stage of wound healing the scab regain sloughs off and retain the normal thickness. Fibrosis is the process of formation of scars. Topical antimicrobial therapy or applying ointment on the wound is one of the common and good method of wound healing. The topical application helps to the attack microbes in wounds and medicinal plants are mostly employed in the wound care (Odimegwu et al 2008).

1.13.8 Factors Effecting Wound Healing

In fact, there are many factors can lead to wound healing. Factors that are directly influence the characteristics of the wound itself are categorized as local factors and systemic factors.

1.13.8.1 Local Factors

The different kind of local factors are;
• **Desiccation:** The wet wounds allow the fast healing and in the dry environment, the wound gets de-hydrated and die.

• **Infections:** Any infections present in the body causes the slow down of the wound healing process. If infection are there in the body along with the wound should be reported to a doctor. The infection is treated with the help of antibiotic therapy which helps to heal the wound and infections.

• **Maceration:** urinary and fecal infections can alter the wound. Awareness about skin protection helps wound management.

• **Necrosis:** There are two types" necrotic cells: slough and eschar. Where the slough is the wet and yellow in colour,. eschar is dry necrotic tissue, and it is in black in colour.

• **Pressure:** Pressure in the capillaries may be disrupted and when the pressure in the wound reduces the wound healing.

• **Trauma and Edema:** These two local factors depends upon the environment, in which wound is repeatedly traumatized due to the edema.

1.13.8.2 Systemic Factors

The different stages of systemic factors are; age, body type, chronic disease, immune-suppression, radiation, laboratory values, nutritional values and vascular effiency.

1.13.9 Screening Methods for Wound healing

For studying the wound healing activity various animals are utilized including rabbits, rats, guinea pigs, goats and other large veterinary animals. Basically the models used includes excision, incision, burn and dead space wounds which usually covers almost all kinds of possible wounds one can encounter in clinical practice. However, specialized models like septic wounds, lacerated wounds, foot lesions, abscess and diabetic wounds are utilized for determining the effectiveness of the drugs in specific clinical situations (Kiran 2008).

1.13.9.1 Excision Wound

In this model, a standard wound is made by cutting a circular skin in the dorsal thoracic region of the experimental animals. Usually a wound of 2.5cm in diameter is made with the help of marking the margin on pre-shaved area with an indelible ink and rubber seal. The wound measurements can also be carried out by putting sutures on the margin of the wound or after tattooing or after making the margin with indelible ink (Kishore et al 2010).
1.13.9.2 Incision Wound

This wound is created by giving straight incision of 6 cm length on pre-shaved skin on the experimental animals with a help of a sharp blade. After bleeding the cut is cleaned. These are caused by making one paravertebral. Following haemostasis, wounds are cleaned of blood with sterile wet cottons. The sutures used to close wounds are made of zero number silk threads placed at slightest 1 cm to one side from each suture. On 9th day the sutures were detached and the wound’s tensile-strength was calculated by the constant water-flow method of Lee. This method indirectly estimates the extent of wound healing that is, more the wound tensile strength more is the deposition of collagen in the wound area (Kalyon et al 2009).

1.13.9.3 Burn Wound

The chemicals, radiations and thermal contact are creating burn wounds. Thermal burns produce a zone of necrosis that includes dead cells and denatured connective tissues.

1.13.9.4 Dead Space Wound

Deposition of granuloma is a vital step in wound healing and the rate of granulation can be directly correlated to the wound healing. Hence, measurement of extent of the granuloma deposition in dead space wounds serves as a meaningful parameter. The granulation tissue may be grown on foreign bodies like sterile cotton pellets, grass piths or polyvinyl sponges. On the materials that are implanted subcutaneously, granulation tissue grows and can be removed and extent of formation of granulation serves as a parameter to measure the wound healing activity (Nayak et al 1999).

1.13.10 Nutritional impact on the Phases of wound healing

Wounding, haemostasis, inflammatory phase, proliferative phase and remodeling are the phases of wound healing. Each phase requires nutrients to accelerate the wound healing process. Nutrients which help in the wound healing is shown in the Table 12.

Nutritional deficiencies can result interruption in wound healing and nutritional facts required for wound repair may decrease healing time. It is hence fundamental and imperative to study the nutritional factors that support wound healing with minimal time scarring, discomfort and pain. Vitamins and minerals are a vital role in wound healing.
Table 12  Nutrients Required for the Phases of Wound Healing

<table>
<thead>
<tr>
<th>Wound healing stages</th>
<th>Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heamostasis</td>
<td>Drugs, herbs, amino acids, vitamins, minerals</td>
</tr>
<tr>
<td>Inflammatory Phase</td>
<td>Vitamin A, Bromelain, Vitamin C</td>
</tr>
<tr>
<td>Proliferative Phase</td>
<td>Vitamin C, Glucosamine, Vitamin A, Zinc</td>
</tr>
<tr>
<td>Remodeling</td>
<td>Protein</td>
</tr>
</tbody>
</table>

1.13.10.1 Vitamin A

Vitamin A improves survival in surgically induced abdominal sepsis and exact non-steroid persuaded post-operative immune depression. Vitamin A is obligatory for epithelial and bone tissue growth, cellular discrimination and immune system role. Vitamin A is used as preoperative nutritional supplement. At the site of wound Vit A increases the count of macrophages and monocytes, modulating collagenase, improving localization, motivation of the resistant response and underneath the epithelial cell differentiation.

1.13.10.2 Vitamin C

Ascorbic acid is essential for the hydroxylation of lysine and proline, reduces the procollagen. Procollagen that is needed for its discharges and subsequent conversion to collagen. Ascorbic acid is an imperative cofactor for the synthesis of proteoglycans and collagen, and assorted normal compounds of the intra-cellular medium of tissues like fur, capillary walls, bones and connective tissues. Clinical manifestations of ascorbic acid deficiency includes poor immunity, bleeding gums, slow healing and easy bruising and fractures. Ascorbic acid increases the neutrophils function and enhances angiogenesis and also increases the collagen production.

1.13.10.3 Vitamin E

The upshot of this vitamin i.e.E, on wound healing is a composite reaction. It may have a vacillation produce array of wounds and nearby will be unlike functions for water soluble against lipid soluble preparation of Vitamin E. The antioxidant membrane stabilizing
consequence of Vit E includes lysosomal membrane stabilization (a function shared by gluco-
corticoids). Vitamin E is well-liked amongst regulars for skin heed and to pass up scar
configuration. It functions as the chief lipophilic antioxidant, preventing the per-oxidation of
fats and more stability in the cell membrane.

1.13.10.4 Zinc

Zinc concern is considered to be in the uppermost appearance, during the pre-
maturational inflammatory stages of wounding. Sequential alter in the zinc concentration where
deliberate in the incision wound model in the rat. Zinc level amplified from wounding and
picked on the fifth time of elevated inflammation granulation tissue formation, proliferation
and epidermal cells. Zinc absorption returned to usual by the seventh day, when the swelling
had been relapse. It have to be suggested that improves local demands for zinc resulting from
surgery and wounding state or else small zinc deficiency in human. Zinc deficiencies had
been allied with the deprived wound healing diminish breaking force of the animal wounds,
which results in decreased collagen creation all through curative originate in zinc deficient
animals.

1.13.11 Dietary supplements and amino acids help in wound healing process

Amino acids and dietary supplements that help the wound healing activity are
- Bromelain
- Glucosamine
- Proteins
- Arginine
- Glutamine

1.13.11.1 Bromelain

Patients with long bone fracture administrated with proteolytic enzyme
combination 90 milligram tablet had a lesser amount of post functioning swelling compared
to patients given placebo. The well-organized orally administered. Bromelain include the
following advantages; decrease swelling, streak, ache, and curative time following distress
and operative actions. Bromelain is a general name specified for the proteolytic enzyme from
pineapple.
1.13.11.2 Glucosamine

Manufacture of hyaluronic acid by fibroblast during the proliferative phase of wound healing encourages the mitosis and migration of the fibroblasts epithelial cells. Glucosamine appears to be rate-limiting substrate for hyaluronic acid synthesis. Hyaluronic acid is an essential part of the extra-cellular matrix and one of the main glycosamino-glycans concealed for the period of tissue repair.

1.13.11.3 Proteins

Protein reduction appear to hinder wound healing by extending the inflammatory stage by reducing fibroplasias, collagen and petroglycans synthesis and neoangigenesis ie proliferation and inhibiting wound remodeling. Amino acids are very essential for the wound healing process in our body.

1.13.11.4 Glutamine

This is an additional amino acid that can develop in to a conditionally essential in certain condition such as tissue damage or injury. Glutamine is used by the cells as which are inflammatory cells as source of energy. Fibroblasts utilize this amino acid for protein and nucleic acid synthesis. Glutamine is released from the skeleton muscle following injury or process.

1.13.11.5 Arginine

Arginine shows a noteworthy position in the protein and the amino acid production. Arginine is a non-essential amino acid. In sufficient cells this amino acid seems to be very essential for wound healing and immune system. This non-essential amino acid is obtained from the diet and resulting endogenously from citrulline in a reaction accelerated by the enzyme Arginine synthetase. In Table 13 shows the nutrients and their actions.
Table 13. Nutrients and its Action on the Wound Healing Process

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Improves localization and stimulation of immune response, enhances early inflammatory phase of wound healing and supports epithelial cell differentiation.</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Synthesis of collagen supports immune response, proteoglycans and other organic compounds of the intra cellular matrix.</td>
</tr>
<tr>
<td>Zinc</td>
<td>Required for DNA synthesis, protein synthesis and cell division.</td>
</tr>
<tr>
<td>Protein</td>
<td>Prevents delayed healing and surgical complication</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>Improves the hyaluronic acid construction in the injury</td>
</tr>
<tr>
<td>Bromelain</td>
<td>Healing time and the pain of the injury is reduced.</td>
</tr>
</tbody>
</table>

1.14 Cancer

The cancer cells of each type grow up and extend in different ways and recognized by uncontrolled cell enlargement. This process is regulated, then controlled by the deoxyribonucleic acid (DNA) within each cell. Table 14 shows the common cancer in India is estimated by the year 2015.
Table 14. Common cancer in India: an estimate by 2015

<table>
<thead>
<tr>
<th>Site of cancer</th>
<th>Incident cases (%)</th>
<th>CIR/105</th>
<th>ASR/105</th>
<th>Ratio at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All ages</td>
<td>35-64 years</td>
<td>All ages</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>27,395 (05.9)</td>
<td>3.9</td>
<td>7.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Pharynx‖</td>
<td>39,098 (08.5)</td>
<td>5.6</td>
<td>11.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>30,485 (06.6)</td>
<td>4.4</td>
<td>9.7</td>
<td>6.6</td>
</tr>
<tr>
<td>Lung</td>
<td>43,126 (09.3)</td>
<td>6.2</td>
<td>9.8</td>
<td>9.4</td>
</tr>
<tr>
<td>Oral cavity*</td>
<td>50,174 (10.9)</td>
<td>7.2</td>
<td>17.6</td>
<td>10.3</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>112,680 (21.0)</td>
<td>17.1</td>
<td>39.7</td>
<td>22.8</td>
</tr>
<tr>
<td>Cervix</td>
<td>139,864 (26.1)</td>
<td>21.3</td>
<td>57.4</td>
<td>28.5</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>21,388 (04.0)</td>
<td>3.3</td>
<td>6.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>28,245 (05.3)</td>
<td>4.3</td>
<td>9.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Ovary</td>
<td>30,114 (05.6)</td>
<td>4.6</td>
<td>9.8</td>
<td>6.2</td>
</tr>
</tbody>
</table>

**CIR:** Crude Incidence Rate, **ASR:** Age Standardized Rate,

*Oral cavity includes tongue, lips, floor of the mouth, cheek, gum and palate,

‖ Pharynx includes oro-pharynx, nasal and hypopharynx.

There are cancers which are curable and their treatments are justifiable. List of curable cancers are shown in Table 15.
Table 15. Curable Cancers for Which Treatment Is Justifiable

<table>
<thead>
<tr>
<th>SI.No.</th>
<th>Cancer</th>
<th>Load (%)</th>
<th>Primary Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breast</td>
<td>20</td>
<td>S/RT/CT/HT</td>
</tr>
<tr>
<td>2</td>
<td>Central Nervous System</td>
<td>02</td>
<td>S/RT</td>
</tr>
<tr>
<td>3</td>
<td>Childhood Cancer</td>
<td>05</td>
<td>CT/S/RT</td>
</tr>
<tr>
<td>4</td>
<td>Colon</td>
<td>07</td>
<td>S/ST</td>
</tr>
<tr>
<td>5</td>
<td>Cervix</td>
<td>18</td>
<td>RT/S</td>
</tr>
<tr>
<td>6</td>
<td>Germ Cell Cancer</td>
<td>03</td>
<td>CT/S</td>
</tr>
<tr>
<td>7</td>
<td>Gestational triphoblastic Disease</td>
<td>01</td>
<td>CT</td>
</tr>
<tr>
<td>8</td>
<td>Oral</td>
<td>11</td>
<td>RT/S</td>
</tr>
<tr>
<td>9</td>
<td>Osteosarcomas</td>
<td>02</td>
<td>CT/S</td>
</tr>
<tr>
<td>10</td>
<td>Soft Tissue Sarcomas</td>
<td>02</td>
<td>S/RT</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>

S: Surgery, CT: Chemo-therapy, RT: Radio-therapy, HT: Hormone-therapy

When cancer occurs in our body some functional changes will take place in cells, associated with genes. Table 16 shows the functional changes in the cells leading to cancer and the associated gene.

1.14.1 Aetiology of Cancer

The following factors have been implicated in the aetiology of cancer.

1. Viruses such as Epstein - Barr virus (EBV), Hepatitis B Virus, (HBV) and Human Papilloma Virus (HPV).

2. Habitat and diet; such as low fiber diet; alcohol consumption, high fat and tobacco smoking.
3. Occupational and Environmental hazards: UV radiation, exposure to ionizing and different chemical carcinogens like asbestos, azo-dyes, benzene and polyvinyl chlorides.

4. Use of drugs like alkylating agents and some immune-suppressant.

The functional changes and outcome for the changes are shown in Table 16.

**Table 16. Functional Changes and Outcome of the Cancer**

<table>
<thead>
<tr>
<th>SI.No</th>
<th>Functional Changes</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Self sufficiency in growth factors</td>
<td>H-Ras oncogene</td>
</tr>
<tr>
<td>2</td>
<td>Insensitivity in growth inhibitors</td>
<td>Loss of retino-blastoma protein (pRb)</td>
</tr>
<tr>
<td>3</td>
<td>Limitless proliferation</td>
<td>Telomerase activity</td>
</tr>
<tr>
<td>4</td>
<td>Sustained angiogenesis</td>
<td>Vascular Endothelial Growth Factor (VEGF) activation</td>
</tr>
<tr>
<td>5</td>
<td>Invasive metastasis</td>
<td>Inactivates E-cadherin Promotes cell adhesion Mutation inactivating E-cadherin promote metastasis</td>
</tr>
<tr>
<td>6</td>
<td>Evading apoptosis</td>
<td>Insulin like Growth Factor (IGF) factors</td>
</tr>
</tbody>
</table>

**1.14.2 Characteristics of Cancer Cells**

**1.14.2.1 Uncontrolled Proliferation**

The genetic changes discussed above confer autonomy of growth to cancer cells so that their proliferation is now not subject to normal physiological processes.
a) Growth factors: Insulin Growth Factor (IGF), Epidermal Growth Factor (EGF), Platelet derived growth factor (PDGF). Growth factor action stimulates a quiescent cell (lying in Go phase) to divide i.e to start with G1 phase. Growth factors act through receptor tyrosine kinases.

b) Growth factors pathways: The cytosolic and nuclear transduce. All these pathways eventually lead to transcription of genes that controls the cell cycles.

c) The cell cycle transducers: These are of 2 types

1. Positive regulators of cell cycles control the changes necessary for cell division and are coded with delayed response genes. These include cyclins i.e cyclin dependent kinases (CDKs). The CDKs phosphorylate various enzymes and proteins to coordinate their activities.

2. Negative regulators of cell cycle that modulate the activity of cyclic / cdks complex. These include Rb proteins, p53 proteins and CDK inhibitors. All of these can hold the cell cycle in steady state if any unphysiological event occurs. In normal healthy cells in the steady state the concentration of p53 proteins is low and Rb proteins exist in phosphorylated form. But if there is DNA damage, p53 proteins accumulate and activate transcription of genes which code on p21 protein. Latter they inactivate cyclin complexes and prevent phosphorylation of Rb proteins. Thus cell cycle is arrested at the first check point only to allow for DNA repair. If repair is not done p53 gene on p53 protein would trigger apoptosis (cell suicide)

d) Disposal of abnormal cells by apoptosis: It is a programmed cell death. Development of resistance to apoptosis or activation of antiapoptotic factors is the main cause of development of cancer. Apoptosis prevents cancer by monitoring the cancerous changes as it acts as first line defense against mutations- disposing cells with abnormal DNA that could become malignant.

e) Tumour directed angiogenesis of blood vessels: This factor influences the total tumour mass because the growth of solid tumour rely on the expansion and amount of
blood supply in to it (angiogenesis), in response to vascular endothelial growth factor (VEGF) produced by growing tumor.

f) Telomerase expression: telomeres are the protective caps over the distal extremity of a chromosomal arm. Telomers protect the chromosomes from degradation and enlargement with other chromosomes. Telomers are long in, immortalized cells and markedly short in normal cells, because with every surrounding cell and the splitting of cells in the upper part of telomere gets eroded and ultimately becomes non-functional. This stage the DNA duplication impede and cells becomes aged.

1.14.2.2 De-differentiation

Normally when daughter get matured they eventually differentiate and behave like their parent cell of origin to carry out the predetermined programmed functions cancer cells do not differentiate e.g the cells of pancreatic tumour do not behave as normal pancreatic cell either in function or in morphology.

1.14.2.3 Invasiveness

Normal cells are not found outside their tissue of origin. If any cell accidentally escapes, it would undergo apoptosis and die. The cancer cell because of mutations in their genes, have no such constraint over them and can slip inside the nearby organs.

1.14.2.4 Metastasis

Cancer cells can disseminate to distal organs through blood and lymphatics and grow. Metastasis will be quicker when, the blood vessels are incubed by the tumours. A series of genetic modification confers resistance on them towards normal regulatory factors and enables them to establish “extraterritorially”.

1.14.3 Features of Tumours

1. Abnormal uncontrolled cell division.
2. Dedifferentiation and loss of function
3. Ability to spread to other parts of the body (invasiveness).
4. Metastasis.
1.14.4.1 Types of tumours

Tumours are of two types. They are known as benign and malignant tumours. Both tumours have two parts; called as parenchyma: which is the functional part of tumour and stroma: it is supportive part of tumour.

1.14.4.1.1 Benign tumours

They are slow growing and do not invade other parts of the body. They are removed by normal surgery and does not lead to death.

1.14.4.1.2 Malignant tumours

These are cancerous tumours which are fast growing and invade other body parts. They cannot be removed by surgery as there is no clear demarcation between normal cells and tumour cells. These tumours may lead to death.

1.14.5 Nomenclature

- Benign tumours
  - Benign tumours are known by the suffix „oma” attached to the cell of origin. Example: fibroma, origin is „fibrosis.”

- Malignant tumours
  - Of mesenchymal origin are known as sarcomas.
  - Of epithelial origin are known as carcinomas.
  - Both of them are collectively known as carcinosarcomas.

1.14.6 Carcinogenic agents

Tumours can be induced tumours by two ways. Carcinogenic agents are of two types i.e; chemical agents, physical agents, hormonal and biological agents.

1.14.6.1 Chemical agents

The chemical carcinogens are divided as initiators and promoters.

1.14.6.1.1 Initiators

These chemical carcinogens initiate tumour growth. Example: polycyclic aromatic hydrocarbons (in cigarette smoke), aromatic amines, azodyes, alkylating agents (cyclophosphamide) naturally occurring substances (betel nut and actionymcin-D)
1.14.6.1.2 Promoters

These chemical carcinogens initiate the growth of already present tumours, but itself does not initiate tumour growth example: phenolic compounds, artificial sweeteners (saccharin and cyclamate) and phenobarbital.

1.14.6.2 Physical agents: also leads to cancerous growth.
   a) Radiation.
   b) Mechanical injury of tissues
   c) Ionizing and UV radiation also causes cancer.

1.14.6.3 Hormonal agents

   a) Oestrogen hormone leads to endometrial cancer
   b) Anabolic steroids can cause liver cancer.

1.14.6.4 Biological agents

   a) Stones in the gall blader and urinary tract can lead to cancer.
   b) Viral infections (Herpes virus) also lead to cancer.

1.14.7 Cell Cycle of Cancer cell

A proper understanding of cell cycle is essential for rational use of anticancer drugs. The cells reproduce themselves through cell division.

1. The somatic cell division: It involves nuclear division by mitosis and cytoplasmic division by cytokinesis. The whole process ensures that each daughter cell gets the same number and kind of chromosomes as the original parent cell.

2. The reproductive cell division: By which sperm and egg cells are produced. This division involves a nuclear division called meiosis and followed by cytoplasmic division called cytokinesis.

1.14.7.1 Cell Cycle Phases

Most cells do not divide constantly and spend a varying amount of time in quiescent (calm) state outside the cell cycle. This phase is termed as G₀. Neurons, skeletal muscle and cardiac muscle cells increase in bulk through hypertrophy and spend their life time in G₀ state. The growth factor action provides momentum for the start of cell cycle. Growth factor stimulates production of positive as well as negative regulators of cell cycle.
through signal transduction. The cell cycle, in itself, consists of two major activities; the
interphase \((G_1 \rightarrow S \rightarrow G_2)\) and the cell division.

1.14.7.1.1 Interphase

When the cell is in between one mitosis and the next, it is said to be
interphase, it is during interphase that the replication of chromosomes, centrosomes and
controls occurs. Also the DNA, the RNAs and the proteins, needed to produce structures and
the required for doubling all cellular components (before mitosis), are manufactured.
Interphase consists of three distinct phases: G1, S and G2 phase.

- **G1 phase** is a growth phase during which cells are engaged in growth, metabolism and
production of substances required for forthcoming cell division.

- **S phase** is where DNA and chromosomes are replicated. S-phase is followed by
another growth phase.

- **G2 phase** (is a period between S phase and mitosis) where the cell prepares itself for
mitotic division into two daughter cells. In G1 and G2 phase there are no events related
to chromosomal or DNA replication. These phases simply serves as preparatory ground
or gaps in DNA synthesis.

Cells that are destined to never divide again are permanently arrested in G1
phase; but once a cell enters in the S-phase it is bound to go through the mitosis (M-phase).
The entry of the cell into S-phase or M-phase is further controlled at two check points in the
cell cycle.

1.14.7.1.2 Mitosis (M-phase)

M-Phase (mitosis) or nuclear division is a though a continuous phase, it can
precisely be divided further into four stages.

- **Prophase** (pro = befor): till now, the chromosomes are still in a form of tangled mass
filled inside the nucleus. In prophase they condense into visible chromosomes. Nuclear
membrane now disappears and condensed chromosomes are released into cytoplasm.
Other cytoplasmic structures in like centrosomes, containing centrioles, move to the
opposite poles of the cells and form the mitotic spindle. As spindles extend from pole to
pole, chromosomes are also pushed and distributed to opposite poles of the cell.
• **Metaphase (Meta=after):** in this second stage of mitosis, the centromeres of the chromatid pair line up at the exact centre of the mitotic spindle in an equatorial plane.

• **Anaphase (ana=upward):** in this third stage of mitosis, centromeres divide and identical sets of chromosomes move to the opposite poles of cells. The separated sister chromatids are referred to as daughter chromosomes.

• **Telophase (telo=end):** this end stage of mitosis is essentially the opposite of prophase. Novel nuclear envelope is reformed around chromatin mass. Nucleoli reappear and spindle disappears.

1.14.7.1.3 Cytokinesis (Cytoplasmic Division)

In these stages a division of parental cytoplasm and organelles takes place. A cleavage furrow is formed around the center of cell, which gradually deepens and separates the cytoplasm and the organelles into two equal and different portions. The daughter cell may now undergo differentiation or remaining G₀ phase, or if stimulated, may enter into interphase (G₁-S-G₂), mitosis and cytokinesis.

1.14.7.2 Length of Cell Cycle

The length of G phase of cell cycle is highly variable. Typically it takes about 8 to 10 hours but it may be even nonexistent (in rapidly dividing cells), two days, weeks or years (in other types of cells). the S phase takes about 6 to 8 hours; G-phase about 4 to 6 hours and mitosis and cytokinesis about 1 to 7 hours together. The various phases of cell cycle require about 18 to 24 hours in mammalian cells.

1.14.8 Cell Cycle Sites of Anticancer Drugs

Anticancer drugs may also be classified broadly according to their cell cycle cytotoxic effects. Combination of chemotherapeutic agents that are active in different phases of cycle can result in greater cell kill. Anticancer drugs falling into cell cycle specific and cell cycle- nonspecific category are listed below:

1.14.8.1 Cell Cycle- Nonspecific (ccns) Agents

Drugs that are cytotoxic to the cell nonselectively at any point in the cycle are called "cell cycle- nonspecific drugs ".

Department of Pharmacy, JFT University, Rajasthan
- **Alkylating agents:** busulfan, carmustine, lomustine, chlorambucil, cylophosphamide, melphalan, dacarbazine, mechlorethamine, ifosfamide and thiotepa etc.
- **Anticancer antibiotics:** dactinomycin, mitomycin, daunorubicin, idarubicin, doxorubicin and mitoxantrone etc.
- **Miscellaneous agents:** hydroxyurea, cisplatin, carboplatin, oxaliplatin and procarbazine etc.

1.14.8.2 Cell Cycle Specific (ccs) Agents

The cell cycle specific drugs exhibit phase selectivity as noted as:

- **G\_1**- **Phase:** asparaginase and steroids.
- **S** – **Phase:** these include Antimetabolites: methotrexate, mercaptopurine, thioguanine, fludarabine, pentostatin, gemcitabine, capecitabine; Camptothecins: topotecan and irinotecan.
- **G\_2** – **Phase:** these include Anticancer Antibiotics: bleomycin, Epipodophyllotoxins: etoposide, teniposide.
- **M**- **Phase:** these include taxanes: paclitaxel and docetaxel; vinca alkaloids: vincristine, vinblastine and vinorelbine

1.14.9 Pathology of Cancer

When the normal cells DNA or blue prints within the cells are damaged, cancer will occur in our body. DNA damage may occur by the exposure to some toxins like cigarette smoke inherited from parents or any spontaneous problem that occurs during the lifetime of an individual. As the cells multiply, they form tumors and these tumors are not cancerous, which grow very large and press on healthy tissues organs and are not life threatening. Tumors, which are cancerous, are called malignant tumors; they will invade other organs or spread via lymphatic channel and are threatening to the life. The scientific researchers are making most excellent hard work to combat this sickness (*Armstrong 1997, Ritesh 2010, Sodde 2011, Manna *et al* 2000).
1.14.10 Cancer Symptoms

Body weight loss is most visible symptom of cancer. Other common and typical symptoms of cancer are; an unusual lump in the body, changes in a mole on the skin, cough and cold, mild or high fever, constipation, diarrhoea, ulcer in mouth or stomach, blood in urine or faeces, difficulty in consuming or swallowing food, any abnormal bleeding through vagina, difficulty to eat, sever pain, vomiting, rashes in skin, change of colour and texture of the skin and sweating at night.

1.14.11 Risk Factors for Cancer

Cancer is also produced by both external factors and internal factors. The numerous agents capable of producing neoplasia naturally and experimentally are carcinogenic chemicals, radiation, oncogenic viruses and environmental factor (Goyal 2007). Risk factors in liver include, chronic liver damage, occupational exposure toward thorium dioxide or vinyl chloride, aflatoxin ingestion and tobacco use. Respiratory system affected by cancer due to tobacco smoking and excessive exposure to ultraviolet radiation.

1.14.12 Diagnosing the Disease

The diagnosis of cancer relies on the procurement of a sample and pathologic assessment of the sample and can be obtained by numerous methods, including biopsy, or fine-needle aspiration. A tissue diagnosis is essential, because many beginning conditions can masquerade as cancer. Early detection of cancer disease improves the success of treatment and survival of the patient. Biopsy is a procedure and absolute way to detect the cancer where, the cancer cells are extracted and examined them under a microscope.

1.14.13 Prognosis of Cancer

The outcome or probable course of cancer is called as prognosis. Many factors help to determine the prognosis and it helps the doctor to plan the cancer treatment. Example prognosis factors are age, size of tumor, physical fitness, stage of cancer and genetic make-up.

1.14.14 Chemotherapy of Cancer (Neoplasms)

Chemotherapy is the most common method for anticancer treatment. This is a treatment of cancer by chemicals. Most anticancer drugs are damage DNA and are anti-proliferative drugs and they will be initiate apoptosis. They also affect rapidly dividing
normal cells and are thus likely to depress bone marrow, depress growth. Most of the drugs will have side effects like vomiting, nausea, hair loss, teratogenicity and sterility. Chemotherapeutic agents used for cancer are alkylating agents, anti-metabolites, plant alkaloids and terpenoids, vinca alkaloids, podophyllatoxin, taxanes, topoisomerase inhibitors, antitumor antibiotics. Neoplasm or tumour is defined as growth or mass of abnormal tissue formed due to excess and uncoordinated cell proliferation (Chemotherapy 2008).


Cancer chemotherapy is aimed either to kill cancer cell or modify their growth. The anticancer drugs generally attack the metabolic sites they are essential in cell replication. For example, these drugs reduce the availability of purine and pyrimidine precursors that are used in synthesis of DNA or RNA. In some non curative cases of cancer, drugs are used for palliation (alteration of symptoms or avoiding life threatening toxicity) or as and adjuvant to surgery or radio therapy and immunotherapy. The drug used in chemotherapy of cancer destroys the constant fraction of malignant cells. Thus a dose which kills 99.999% of cells, if used to treat a tumour of 10⁹ cells, will still leave 10⁴ viable malignant cells. At this point the patient becomes asymptomatic and remission occurs later. Some malignant cells also find safe places such as CNS, where certain chemotherapeutic agents can not attack. Some drugs may be unable to penetrate certain areas of solid tumours. These are the major difficulties in the use of drugs for cancer.

The tumor cells that are in replicative cycle are more susceptible to chemotherapeutic agents. Rapidly dividing cells are more sensitive and the non proliferating cells survive to the toxic effects of these agents. The growth of tumour cells does not usually occur in exponential rate. In case of most of the solid tumours, the growth rate decreases as the tumour size increases because of the decrease in ability of blood supply resulting in unavailability of nutrients and oxygen. The currently used chemotherapeutic agents are effective against the dividing cells in solid tumours and hence the resting cells in the tumour produce a problem in treatment.
1.15 Classification of Anticancer Drugs

Classification of anti cancer drugs is given Table 17 and site of action of these agents is shown in Fig 6.

Table 17. Classification of Anticancer Drugs

<table>
<thead>
<tr>
<th>A. Drugs acting directly on the cell Cytotoxic drug</th>
<th>Sub category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sl No.</td>
<td>Category</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alkylating agent</td>
<td>Nitrogen mustard</td>
</tr>
<tr>
<td></td>
<td>Ethylenimine</td>
<td>Thio-TEPA</td>
</tr>
<tr>
<td></td>
<td>Alkyl sulfonate</td>
<td>Busulfan</td>
</tr>
<tr>
<td></td>
<td>Nitrosoureas</td>
<td>Carmustine, Lomustine</td>
</tr>
<tr>
<td></td>
<td>Triazine</td>
<td>Dacarbazine</td>
</tr>
<tr>
<td>1</td>
<td>Antemetabolites</td>
<td>Folate antagonist</td>
</tr>
<tr>
<td></td>
<td>Purin antagonist</td>
<td>6-Mercaptopurine, 6-Thioguanine, Azathiopurine</td>
</tr>
<tr>
<td>2</td>
<td>Pyrimidine antagonist</td>
<td>5-Fluorouracil, Cytarabine</td>
</tr>
<tr>
<td>3</td>
<td>Vinca Alkaloids</td>
<td>Vincristine, Vinblastine</td>
</tr>
<tr>
<td>4</td>
<td>Taxanes</td>
<td>Paclitaxel, Docetaxel</td>
</tr>
<tr>
<td>5</td>
<td>Epipodophyllotoxin</td>
<td>Etoposide</td>
</tr>
</tbody>
</table>
## Introduction

<table>
<thead>
<tr>
<th>6</th>
<th>Camptothecin Analogues</th>
<th>Topotecan, Irinotecan</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Antibiotics</td>
<td>Actinomycin D, Doxorubicin, Daunorubicin, Mitoxantrone, Bleomycins, Mitomycin C, Mithramycin</td>
</tr>
<tr>
<td>8</td>
<td>Miscellaneous</td>
<td>Hydroxyurea, Procarbazine, L-Asparaginase, Cisplatin, Carboplatin</td>
</tr>
</tbody>
</table>

### B. Drugs altering hormonal milieu

<table>
<thead>
<tr>
<th>1</th>
<th>Glucocorticoids</th>
<th>Prednisolone and others</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Estrogens</td>
<td>Fosfestrol, ethinylestradiol</td>
</tr>
<tr>
<td>3</td>
<td>Antiestrogens</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>4</td>
<td>Antiandrogen</td>
<td>Flutamide</td>
</tr>
<tr>
<td>5</td>
<td>5-α. Reductors inhibitor</td>
<td>Finasterade</td>
</tr>
<tr>
<td>6</td>
<td>GnRH analogues</td>
<td>Naferelin, Goserelin</td>
</tr>
<tr>
<td>7</td>
<td>Progestins</td>
<td>Hydroxyprogesterone acetate.</td>
</tr>
</tbody>
</table>
**Introduction**

**Fig 6. Site of Action of Anticancer Drugs**

- **PENTOSTATIN** inhibits adenosine deaminase
- **6-MERCAPTOPURINE** and **6-THIOGUANINE** inhibit purine synthesis and nucleotide interconversion
- **METHOTREXATE** inhibits dihydrofolate reduction; blocks dTMP and purine synthesis
- **CYTARABINE, FLUDARABINE, GEMCITABINE** inhibits DNA synthesis
- **BLEOMYCIN** prevents DNA repair/synthesis in G2 phase
- **TOPOTECAN, ETOPOSIDE, TENIPOSIDE, DOXORUBICIN, DAUNORUBICIN** inhibit topoisomerase action and RNA
- **L-ASPARAGINASE** deaminates asparagines and inhibits protein synthesis
- **IMATINIB** etc., Inhibit protein kinase activity.
- **BORTEZOMIB** is a proteasome inhibitor. They block enzyme action and signaling pathway

**Purine Synthesis**

**Pyrimidine synthesis**

**HYDROXYUREA** inhibits ribonucleotide reductase

**5-FLUOROURACIL** inhibits dTMP synthesis

**DEOXYRIBONUCLEOTIDE**

**DNA**

**ALKALYTING AGENTS, CISPLATIN, ANALOGUES, MITOMYCIN** alkylates

**RNA**

- t-RNA, m-RNA or r-RNA

**Proteins**

**MICROTUBUL**

**ENZYMES** etc.

**Vinca Alkaloids** and **Taxanes** inhibit microtubule functioning

**Transcription of genes**

**Arsenic Trioxide** and **Vorinostat** promote transcription of proapoptotic genes
1.14.15.1 Alkylating agents

Alkylating agents contain chemical groups that produce highly reactive carbonium ion intermediates that can form covalent bonds with particular nucleophilic, substances in the cell. These ions are highly reactive with electron donors such as amine, hydroxyl and sulphhydryl group. The nitrogen at position 7 (N-7) of guanine residues in DNA is strongly nucleophilic and it is especially susceptible. Other molecular sites such as N-1 and N-3 of adenine and N-3 of cytosine may also be affected.

Most of the alkylating agents are bifunctional (have 2 alkylating agents) and are able to react with two groups causing intra or inter chain cross linking. This can interfere not only with transcription but also with replication. Thus alkylation may result in cross linking, chain scission or abnormal base pairing (substitution of GC pair by AT pair). Alkylating agents can also produce cross linking of nucleic acids with proteins.

Alkylating agents mainly exert cytotoxic actions. Some of the alkylating agents are CNS stimulant, immuno-suppressant and cholinergic properties. Nitrogen mustards have radiomimetic (like ionizing radiation) properties. These agents depress bone marrow function and cause gastrointestinal problems. Prolonged use may impair spermatogenesis irreversibly in males and may cause amenorrhoea and fetotoxicity in females. They also increase the risk of acute non-lymphocytic leukaemia and other malignancies.

1.14.15.1.1 Mechlorethamine (mustine)

Mechlorethamine is the first nitrogen mustard used in cancer chemotherapy. It is used as local vesicant in tissues of skin, eyes and respiratory tract. The drug undergoes an intramolecular cyclisation losing chlorine ion and forms a reactive intermediate that interact with DNA and other molecules. The drug is very unstable in water and should be made into solution prior to administration. The drug is administered only intravenously, because it can cause severe irritation, necrosis and sloughing. It is metabolized in the body and is excreted in urine.

The common unwanted effects produced by mechlorethamine are anorexia, nausea and vomiting. It may also cause bone marrow depression and latent viral infections due to immunosuppression. Mechlorethamine is mainly used in treatment of Hodgkin"s disease and also for solid tumours. It is used as combinational regimen (MOPP) in Hodgkin"s
disease. Estramustine is a combination of estrogen and mustine both of which have cytostatic and hormonal effects. It is mainly used in treatment of prostate cancer.

1.14.15.1.2 Cyclophosphamide

Cyclophosphamide is a form of prodrug which is transformed into active metabolites (aldophosphamide, phosphoramid mustard) in liver. It has actions similar to that of mechlorethamine. The active metabolites exert a cytotoxic action. Cyclophosphamide can be administered orally or intravenously. The metabolites are excreted in minimal quantities into faeces or urine. The major unwanted effects of the drugs are nausea, vomiting, bone marrow depression and haemorrhagic cystitis.

Haemorrhagic cystitis is caused by a metabolite acrolein in the epithelium of urinary tract. This can be minimised by increasing fluid intake and administering sulphhydryl donor compounds such as N-acetylcysteine or mesna (sodium-2-mercaptopethane sulphonate). These agents inactivate the acrolein, forming a non-toxic compound. Cyclophosphamide is used in combination regimens to treat various malignancies. It is also used to treat chronic lymphatic leukaemia, lymphoma and solid tumours. It is also used as immunosuppressive agent.

1.14.15.1.3 Ifosfamide

Ifosfamide is a congener of cyclophosphamide. It is similar to cyclophosphamide in all aspects but has a longer and dose dependent plasma half-life. It causes less alopecia and is less emetogenic than cyclophosphamide. Chloroacetaldehyde, a metabolite of Ifosfamide causes high incidence of neurotoxicity.

1.14.15.1.4 Chlorambucil

Chlorambucil is the slowly acting nitrogen mustard. It has properties similar to that of mechlorethamine. It is effective orally and is especially active on lymphoid tissue. The drug does not produce local irritation and less likely cause alopecia on prolonged use. It exhibits a dose-dependent myelosuppressive effect. Chlorambucil is the drug of choice in chronic lymphatic leukaemia. It is also used in Hodgkin’s disease and some solid tumours. It also has immunosuppressive property.
1.14.15.1.5 Melphalan

Melphalan is phenyalanine nitrogen mustard. It has properties similar to that of mechloretamine. It is effective orally and is less irritant locally and alopecia is rare. It is very effective in multiple myeloma, breast cancer and advanced ovarian cancer. Infections, diarrhea and pancreatitis are the complications.

1.14.15.1.6 Thiotepa

Thiotepa is an ethyleneimine compound having actions similar to that of mechloretamine. It is not well absorbed orally and is administered intravenously. It is used for superficial bladder tumours.

1.14.15.1.7 Busulfan

Busulfan acts differently from nitrogen mustards. It has a selective effect on the bone marrow, depressing the formation of granulocytes and the platelets in low dosage and RBCs in higher doses. It has little effect on lymphoid tissue and gastrointestinal tract. Unwanted effects are hyperuricaemia and pulmonary fibrosis. It is the drug of choice in chronic granulocytic leukaemia.

1.14.15.1.8 Nitrosoureas

Nitrosoureas (carmustine and lomustine) are lipid soluble alkylating agents. Streptozocin is another nitrosourea that is a specifically tonic to β-cells of the islets of langerhans (pancreas) and is used in treatment of insulinomas. Carmustine is administered intravenously and lomustine is administered orally. Because of lipid solubility, they cross the blood brain barrier and are effective in meningeal leukaemias and brain tumours. Nitrosoureas have cumulative depressive effect on bone marrow and also produces other adverse effects such as nausea, vomiting, visceral fibrosis and renal damage.

1.14.15.1.9 Decarbazine

Decarbazine is a prodrug which is activated in the liver. It mainly inhibits synthesis of RNA and proteins. It is mainly used in malignant myeloma and Hodgkin's diseases. Unwanted effects include myelotoxicity, nausea and vomiting.

1.14.15.2 Antimetabolites

Antimetabolites are structurally related to normal components of DNA or to coenzymes involved in the nucleic acid synthesis. These generally interferes with the
availability of purine and pyrimidine nucleotides precursors by inhibiting there synthesis or by competing with them in DNA or RNA synthesis.

1.14.15.2.1 Folate antagonists

1.14.15.2.1.1 Methotrexate

Methotrexate is the most widely used antimetabolite in cancer chemotherapy. It mainly acts by inhibiting the enzyme dihydrofolate reductase (DHFR), which is essential in synthesis of folate it is cell cycle specific and kills cells in S phase. It mainly inhibits the synthesis of DNA, also affects RNA and protein synthesis.

In addition to cytotoxic action, It also possess immunosuppressive and anti-inflammatory actions.

- **Mechanism of action:** folic acid is essential for the production of the coenzyme, tetrahydrofolic acid (THF). The conversion of folates to THF is carried out by an enzyme, “folate reductase”. Methotrexate competes with folic acid for this enzyme by binding irreversibly to folate reductase, thus inhibiting the production of THF. Lack of the coenzyme THF leads to inhibition of DNA synthesis and consequently of cell replication.

- **Resistance:** resistance to Methotrexate may develop because of increase in levels of dihydrofolate reductase activity, alteration in the structure of enzyme or decrease in transport of Methotrexate into the cell.

- **Pharmacokinetics:** Methotrexate is usually administered orally. It can also be given intramuscularly, intravenously and intrathecally. The drug is mainly concentrated in intestinal epithelium, liver, kidney and skin. It is actively taken up by the cells and is metabolised into polyglutamate derivatives, which are retained in cells for a long time.

- **Adverse effect:** unwanted effects are due to deficiency of folate and include depression of bone marrow and damage to gastrointestinal epithelium. Other unwanted effects include pneumonitis, nephrotoxicity, pulmonary toxicity and neurologic toxicity. The toxicity of Methotrexate can be overcome by administrating folinic acid.
• Clinical uses: it is used clinically for the treatment of acute lymphatic leukaemia, choriocarcinoma and other malignancies. It is also used for the treatment of rheumatoid arthritis, psoriasis and as immuno-suppressant.

1.14.15.2.2 Purine antagonists

1.14.15.2.2.1 6-mercaptopurine

6-mercaptopurine is an analogue of purine and is highly effective anti cancer drug. The drug is converted in the cell to ribonucleotide of six mercaptopurine , which then suppresses the denovo biosynthesis of purine and hence of DNA. It has pharmacological actions similar to that of methotrexate.

The drug is well absorbed on oral administration and is distributed well throughout the body except cerebrospinal fluid. It is metabolized to thiouric acid by xanthine oxidase. When allopurinol (a xanthine oxidase inhibitor) is used by cancer patient to reduce hyperuricemia, the dose of six mercaptopurine should be reduce to avoid accumulation and exacerbation of toxicities.

Mercaptopurine and its metabolites are rapidly excreted by the kidneys, unwanted effects include nausea, vomiting and diarrhea. Bone marrow depression is the main toxic effect produced and hepatotoxicity is also reported. 6-mercaptopurine is mainly used in childhood acute leukaemia, choriocarcinoma and in solid tumours. It is also used in the maintenance of remission in acute lymphoblastic leukaemia.

1.14.15.2.2.2 6–thioguanine

6–thioguanine is an analogue of purine which is highly effective in non lymphocytic leukamie in combination with daunorubicin and cytarabine. The drug has properties and actions similar to that of 6-mercaptopurine. Allopurinol does not increase the level of 6-thioguanine because very little amount of the drug is metabolised into thiouric acid.

1.14.15.3 Pyrimidine antagonist

1.14.15.3.1 5-Fuorouracil

5-fluorouracil is an analogue of uracil (pyrimidine), 5-fluorouracil must be converted in the body to the corresponding deoxynucleotide (5-fluoro-2-deoxy uridine monophosphate), which inhibits thymidylate synthesis and blocks the conversion of
deoxyuridilic acid to deoxythimidylic acid. The result is inhibition of DNA synthesis but not RNA or protein synthesis. Fluorouracil itself gets incorporated into nucleic acid which may contribute to its toxicity.

5-fluorouracil is administered intravenously to prevent first pass metabolism. It is well distributed in the body including CNS. It is mainly metabolized in liver and dosage must be adjusted in case of impaired hepatic function. Unwanted effects include gastrointestinal disturbances, ulcers in GIT, bone marrow depression and anorexia. Cerebellar disturbances can also occur. The drug is mainly used in solid tumours of breast, colon, urinary bladder, liver etc. it is also effective in treating superficial basal cell carcinomas by topical application.

1.14.15.3.2 Cytarabine (cytocine arabinoside)

Cytarabine is an analogue of the nucleoside 2'-deoxyctydine and acts as pyrimidine antagonist. It is a phosphorylated in the body to cytosine arabinoside triphosphate, which inhibits DNA polymerase. It may also get incorporated into DNA and terminate chain elongation. It is usually administered intravenously and gets distributed well in the body except CNS.

It is metabolized by oxidative deamination and is excreted by the kidney. Unwanted effects include bone marrow depression and gastrointestinal disturbances. Hepatic dysfunction and cerebellar ataxia can also occur. Cytarabine is mainly used in acute non lymphocytic leukaemia in combination with 6-thioguanine and daunorubicin. It is also used in Hodgkin”s disease and non-Hodgkin”s lymphoma.

1.14.15.4 Plant Derivatives

1.14.15.4.1 Vinca alkaloids

Vincristine, vinblastine and vindesine are the main vinca alkaloids used in cancer chemotherapy. These are obtained from the plant vinca rosea. These act by inhibiting mitosis. They bind to tubulin and inhibit its polymerization into microtubules and thus prevent spindle formation in mitosing cells and cause arrest of metaphase. Hence, they are both cycle specific and phase-specific.

Vinca alkaloids are usually administered intravenously. They are mainly concentrated and metabolized in the liver and are excreted into bile and through faeces. The
dosage must be modified in patients with impaired hepatic function. They exert a rapid cytotoxic effect and cell destruction which cause hyper uricaemia due to oxidation of purines to uric acid. This can be reduced by taking allopurinol (xanthine oxidase inhibitor). Common unwanted effects include nausea, vomiting, diarrhea and alopecia. Vincristine has mild myelosuppressive activity but causes paraesthesia and muscle weakness. Vinblastine is more potent myelosuppressant and less neurotoxic but causes leucopenia. Vindesine has both moderate myelotoxicity and neurotoxicity.

Vincristine is mainly used in treatment of childhood acute leukaemia. It is also used in lymphosarcoma, Hodgkin’s disease, wilm’s tumour, Ewing’s sarcoma and carcinoma lung. Vinblastine is used in combination with bleomycin and cisplatin for treating Hodgkin’s disease and testicular carcinoma.

1.14.15.4.2 Taxanes

1.14.15.4.2.1 Paclitaxel

Paclitaxel is obtained from the bark of the western yew tree. The drug reversibly bind to the tubulin and results in the formation of stable non functioning microtubule by promoting polymerization and stabilization of the microtubules. Thus, it interferes with mytosis causing the death of the cell. Paclitaxel is administered by intravenous infusion. It is metabolized in liver and is eliminated in bile. Dosage should be modified in patients with dysfunction and renal impairment.

Unwanted effects include bone marrow toxicity and cumulative neurotoxicity. Other unwanted effects include asymphomatic bradycardia, alopecia, skin rashes and hypersensitivity reactions. Paclitaxel is mainly used in metastatic carcinoma of ovary and ovarian and breast. It is also effective against advanced cases of head and neck cancer, small cell lung cancer, esophageal adenocarcinoma and hormone refractory prostate cancer.

1.14.15.4.2.2 Docetaxel

Docetaxel is an analogue of paciltaxel with some mechanism of action. It also has similar properties but alonger half-life than paciltaxel. It is administered orally and its uses are same as that of paciltaxel.
1.14.15.4.3 Etopodophyllotoxins

1.14.15.4.3.1 Etoposide

Etoposide is a semisynthetic derivative of podophyllotoxin obtained from podophyllum peltatum. It mainly acts by inhibiting the enzyme topoisomerase II, leading to DNA damage. It blocks cells in the late S-G2 phase of the cell cycle. Etoposide can be administered orally or intravenously. It is highly bound to plasma proteins and is distributed well in the body except CNS. Metabolites are converted to glucuronide and sulphate conjugates and are excreted in the urine.

The main unwanted effects include nausea, vomiting, alopecia and myelosuppression. Anaphylactic reactions and hypotension may also occur. Etoposide is mainly used in testicular tumours, lung cancer, Hodgkin’s disease and carcinoma bladder.

1.14.15.4.4 Camptothecins

Topotecan and irinotecan are the main camptothecin analogues obtained from Chinese tree „Captopreca acuminata”. They mainly act by inhibiting the enzyme topoisomerase I, leading to inhibition of DNA replication. They act in the S phase and arrest cell cycle at G2 phase.

1.14.15.4.5 Topotecan

Topotecan is used in metastatic carcinoma of ovary and small cell lung cancer after failure of primary chemotherapy. The main unwanted effects are myelosuppression, neutropenia and gastrointestinal disturbances.

1.14.15.4.6 Irinotecan

Irinotecan is a prodrug which is decarboxylated in liver to active metabolite. It can also inhibit acetylcholinesterase enzyme and hence produce cholinergic effects. It is mainly used in colorectal carcinoma and cancer of lung, cervix, ovary etc. Adverse effects include diarrhea, neutropenia, thrombocytopenia, haemorrhage and body aches.

1.14.15.5 Antibiotics

1.14.15.5.1 Dactinomycin (Actinomycin D)

Dactinomycin is a very potent antineoplastic antibiotic obtained from the species of streptomycin. The drug intercataslyates into the minor groove of double helix between guanine-cytosine base pairs of DNA and interferes with the movement of RNA
polymerase along the gene and thus preventing transcription. It may also cause strand break and stabilize DNA-topoisomerase II complex.

Dactinomycin is administered intravenously and is mainly concentrated in the liver. It do not cross blood-brain barrier (BBB). It is partially metabolized in liver and is excreted in bile and urine. Unwanted effects include vomiting, stomatitis, diarrhea, erythema, alopecia and bone marrow depression. It can damage the skin that is exposed to radiation. Extravasation also produces serious problem.

Dactinomycin is effective in combination with methotrexate against gestational choriocarcinoma. It is also used in combination with surgery and vincristine for treatment of wilm’s tumour and some soft-tissue sarcomas.

1.14.15.5.2 Doxorubicin and daunorubicin (Rubbidomycin)

Doxorubicin and daunorubicin are anthracycline anthracycline antibiotics with quite similar structure. These antibiotics bind to DNA and inhibit both DNA and RNA synthesis. They produce breaks in DNA strands by activating topoisomerase II and generating semiquinone free radicals. The semiquinone radicals reduce molecular oxygen to superoxide ions and hydrogen peroxide that mediates single strand scission of DNA. These antibiotics are administered intravenously. Extravasation can lead to tissue damage.

They bind to plasma protein and are well distributed in the body except CNS. They are metabolized and excreted in bile and urine. The drugs import a red color to the urine. In addition to general unwanted effect, these produce cardiotoxicity and alopecia. Doxorubicin is widely used for treatment of sarcomas and a variety of carcinomas including breast, lung. Acute lymphocytic leukaemia and lymphomas. Daunorubicin is used for treatment of Acute lymphocytic and leukaemias.

1.14.15.5.3 Mitoxantrone

Mitoxantrone is structurally related to doxorubicin. It produces low cardiotoxicity and also has narrow range of utility. It is used in acute non haemolytic leukaemia, non-Hodgkin lymphoma and carcinoma breast. It causes dose related cardiotoxicity and myelosuppression.
1.14.15.5.4 Bleomycins

Bleomycins are a group of metal-chelating glycopeptides antibiotics, obtained from streptomyces verticillus with potent antitumour activity. These antibiotics degrade preformed DNA, causing chain fragmentation and release of free bases. This action is produced by chelation of copper or iron ions which produces superoxide ions that intercalates between DNA strands causing chain scission. It is most effective in \( G_2 \) phase of cell cycle and mitosis.

Bleomycins can be administered by many routes. The enzyme which inactivates bleomycin (hydrolose) is high in many tissue, but low in lungs and skin, accounting for its toxicity in these tissues. Most of the drug is excreted unchangedly in urine. The most serious unwanted effect is pulmonary fibrosis. Mucocutaneous reactions, alopecia, allergic reactions are common. Bleomycin is mainly used in the treatment of testicular tumours in combination with vinblastine or etoposide. It is also highly effective in squamous cell carcinoma of skin, oral cavity, head, neck, genitourinary tract, esophagus and Hodgkin's lymphoma.

1.14.15.5.5 Mitomycin

Mitomycin is obtained from streptomyces caesipitous. It is highly toxic drug used in resistant cancer of stomach, cervix, colon, rectum and bladder etc. It is activated by enzyme in the cell and act as a bifunctional alkylating agent, alkylating mainly at 6 of guanine. It cross-links DNA and may also, degrade by generating free radicals. Bonemarrow depression, gastrointestinal disturbances, kidney damage and pulmonary fibrosis are main unwanted effects.

1.14.15.6 Hormones

Hormones are not cytotoxic, but they can inhibit the growth of tumours with opposing actions by hormones antagonist or by agents that inhibits synthesis of the relevant hormones. They modify the growth of Hormone-dependent tumours.

1.14.15.6.1 Glucocorticoids

Glucocorticoid has lymphocytic action and is used in leukaemias and lymphomas. They have a secondary role in some hormone responsive breast cancers. They are also used in a supportive role in other cancer treatment for symptomatic relief by
antipyretic, mood elevating and raised intracranial pressure. Prednisolone and dexamethasone are most commonly used.

1.14.15.6.2 Estrogens

Estrogens such as fosfestrol produce symptomatic relief in prostatic tumours, which is an androgen-dependent tumour. Fosfestrol is activated by acid phosphate in prostatic tissue and blocks the effect of androgens. Use of Estrogens is superseded in prostatic tumours by gonadotrophin-releasing hormone analogues and antiandrogens.

1.14.15.6.3 Progestins

Progestins such as megestrol and medroxyprogesterone are used in endometrial neoplasms and renal tumours to bring temporary remission. These are also used in palliative treatment of metastatic breast cancer.

1.14.15.6.4 Gonadotrophin-Releasing Hormone Analogues

GnRH analogues such as goserelin indirectly inhibit secretion of estrogen or androgens by suppressing gonadotrophin release. It can be used in advanced breast cancer in premenopausal woman and in prostate cancer. Octreotide (somatostatin analogue) is used to treat various hormone-secreting tumours of GIT such as VIPomas, glucagonomas, carcinoid syndrome and gastrinomas.

1.14.15.6.5 Anti-estrogens

Tamoxifen, an anti-estrogen is effective in hormone-dependent breast cancer. In breast tissue, tamoxifen depletes the estrogen receptor and the growth-promoting effect of the hormone is suppressed. It also has protective activity against heart disease and osteoporosis due to its ability to decrease low density lipoproteins (LDL) and increases bone mineralization.

1.14.15.6.6 Anti-Androgens

Flutamide and cyproterone are androgen antagonists used in prostate tumours. As these increases androgen levels they are administered with GnRH analogues to produce full effect.
1.14.15.7 Miscellaneous Drugs

1.14.15.7.1 Hydroxyurea

Hydroxyurea is mainly used in treatment of myeloproliferative disorders. It act by blocking the conversion of ribonucleotide to deoxyribonucleotides by inhibiting the enzyme ribonucleoside diphosphate reductase, a rate limiting step in DNA synthesis.

Unwanted effects include myelosuppression, gastrointestinal disturbance, alopecia and stomatitis. It is mainly used in the treatment of chronic granulocytic leukaemia, polycythaemia vera, thrombocytosis and some solid tumours.

1.14.15.7.2 Procarbazine

Procarbazine is a methyl hydrazine derivative effective in treatment of Hodgkin’s disease. It inhibits DNA, RNA and protein synthesis. It is a component of „MOPP” [MOPP components are Mechlorethamine (Mustine), Oncovin (Vicristine), Procarbazine (Matulane), Prednisone (Deltasone)] regimen for Hodgkin's disease. It is also used in non-hodgkin's lymphomas and oat cell carcinoma of lungs. It also has a weak MAO (Monoamine Oxidase Inhibitor) inhibitory action and patients should be warned against taking food that contains tyramine. With alcohol it produces a disulfiram-like effect. It is mutagenic and teratogenic. Vomiting, leucopenia, thrombocytopenia and dermatitis are the prominent toxicities.

1.14.15.7.3 L-Asparaginase

L-Asparaginase is an enzyme which deaminates asparagine to aspartic acid and ammonia it is prepared from E.coil. Asparaginase is a non essential amino acid synthesized by mammalian cell. Some tumour cells are unable to synthesize asparagine and depend on the supplies from host.

L-asparaginase acts by depleting aspargine from host, thus depriving the malignant cell from asparagines. Unwanted effects include hypersensitivity, decrease in clotting factors, liver abnormalities, pancreatitis, seizures and coma due to ammonia toxicity. L-asparaginase is mainly used in treating childhood acute lymphocytic leukaemia in combination with vincristine and prednisone. It is also used in reticulum cell sarcoma.
1.14.15.7.4 Cisplatin

Cisplatin is a planar coordination complex containing central platinum atoms surrounded by 2 chlorine atoms and 2 ammonia rations. It is hydrolysed intracellularly to produce a reactive complex which causes intrastrand cross-linking of DNA between N-7 and O6 of adjacent guanine molecules, resulting in denaturation of DNA chain.

Cisplatin produces severe nausea and vomiting so antiemetic should be administered prophylactically. It also produces dose-related unwanted reactions such as renal damage, tinnitus, hearing loss, peripheral neuropathies, hyperuricaemia and anaphylactic reactions. Cisplatin is effective in metastatic testicular and ovarian carcinoma. It is also used for the treatment of many other solid tumours.

1.14.15.7.5 Carboplatin

Carboplatin is a derivative of cisplatin it is used in patients, who can not be vigorously hydrated as it is required by cisplatin treatment or suffering with kidney dysfunction. It produces less nephrotoxicity and ototoxicity (ear toxicity). Nausea and vomiting is mild and is delayed. It is mainly used in ovarian cancer, squamous carcinoma of head, neck, small cell lung cancer and seminoma.

1.14.15.7.6 Imatinib

Imatinib is a tyrosine kinase inhibitor which is effective in chronic myeloid leukaemia. It not only inhibits platelet-derived growth factor (a receptor tyrosine kinase) but also other aspects of signal transduction, specifically a cytoplasmic kinase considered to be factors in the pathogenesis of chronic myeloid leukaemia. Unwanted effects include fluid retention, edema, vomiting, abdominal pain, myalgia and liver damage.

1.14.15.7.7 Radioactive isotopes

Radioactive isotopes are used in the treatment of certain tumours by their property of producing ionization in the cells, there by causing cell destruction. Radioactive iodine (^{131}I) is used in thyroid carcinoma. Radioactive phosphorus (^{32}P) is used in polycythemia vera. Radioactive gold (^{198}Au) is used in palliative treatment of malignant pleural and peritoneal effusions.
1.14.15.7.8 Interferons

Interferons may exert cytotoxic action by stimulating the natural killer cells. Interferon is a potent activator of tumoricidal macrophages. Interferons are mainly used in the treatment of hairy cell leukaemia. It can also be used in squamous cell carcinoma, melanoma and multiple myeloma.

1.14.15.7.9 Monoclonal antibodies

Monoclonal antibodies such as rituximab and trastuzumab are also used in the cancer chemotherapy. These antibodies activate the host immune mechanism and kill the cancer cells. Rituximab is used for β-cell lymphoma and trastuzumab is used for breast cancer treatment.

1.14.15.8 Resistance to Anticancer Drugs

Some neoplastic cells such as melanoma are inherently resistant to many anticancer drugs. Other tumours may acquire resistance during the treatment with the drugs. Acquired resistance may be a result of either adaptation of tumour cells or mutation in the tumour cells. Multidrug resistance is due to ATP–dependent efflux of drug out of the cell associated with the presence of P–glycoprotein. Cross–resistance among structurally unrelated drugs also occurs. There are many other mechanisms which are responsible for the resistances to drugs.

1.14.16 Toxicities of Drugs Used in Cancer Chemotherapy

Chemotherapeutic agents are most toxic to rapidly proliferating cells, such as mucous membranes, skin, hair, GIT and bone marrow. The latter toxicity could be life threatening.

1.14.16.1 Bone Marrow Suppression (Myelosuppression)

Almost all chemotherapeutic agents, except asparaginase, bleomycin, vincristine, gefitinib and some hormones and hormone antagonists, cause myelosuppression. Drugs that can cause severe myelo-suppression include carmustine, cytarabine, daunorubicin, doxorubicin, paclitaxel, alkylating agents and antimetabolites. WBC is most affected because of their shorter life span. A significant decrease is observed, in neutrophile counts (neutropenia) which predisposes the patients to various infections. Colony stimulating factors
can be used to increase neutrophile production and to reduce the degree and duration of neutropenia.

Myelosuppression is the main unwanted effects of anticancer agents. To overcome this problem some of the patient’s bone marrow is removed prior to the cancer chemotherapy, purged (cleansed) it of cancer cells and is replaced after therapy. Harvesting stem cells from blood after administrating molgramostim amand multiplying them in-vitro with relevant heamopoietic growth factors is frequently used now. Platelets have an intermediate life span (less than 10 days) and are affected next. Decreased platelets (thrombocytopenia) can lead to bleeding and may require platelet transfusion or the use of thrombopoietic growth factor, (example oprelvekin or thrombopoietin).

Anemia and fatigue can also occur, but at a later stage because of longer lifespans of RBC’s (120 days). Human recombinant erythropoietin may be used to increase the haemoglobin and to decrease transfusion requirements. In general, onset of myelosuppression takes about 7-10 days from the start of chemotherapy. Lowest counts are reached with in 10-14 days. Recovery occurs after 2-3 weeks of stopping the chemotherapy. Hence the patient’s counts must be sufficiently recovered before receiving the next chemotherapy.

1.14.16.2 Dermatological Toxicity

Many anticancer drugs (ifosfamide, paclitaxel, doxorubicin, vincristine, mechlorethamine, methotrexate and cyclophosphamide) damage hair follicles and produce partial or complete alopecia. Hair usually reappears after completion of chemotherapy. Cancer chemotherapy may cause hyper-pigmentation of skin (bleomycin, 5-fluorouracil, hydroxyurea and methotrexate). Local necrosis may result from extra vacation of some chemotherapeutic agents like dactinomycin, daunorubicin, doxorubicin, idarubicin, mitomycin, vinca alkaloids and monoclonal antibodies.

1.14.16.3 GIT Toxicity

Carmustine, cisplatine, dacarbazine, cyclophosphamide, mechlorethamine, cytrabine, lomustine, doxorubicin and procarbazine are highly emetogenic. They stimulate both CTZ (Chemoreceptor Trigger Zone) as well as vomiting centre. Ondansetron and antihistamines can prevent such type of emesis. Stomatitis is a common toxicity of many
chemotherapeutic agents (eg; capecitabine, 5-fluorouracil). However it resolves in 10 to 14
days of stopping the therapy. Other GI toxicities include constipation, diarrhea, anorexia,
xerostomia and taste changes. Amifostine, a cyto-protective agent can reduce the incidence of
xerostomia.

1.14.16.4 Neurotoxicity

Neurotoxicity can occur not only by intrathecal chemotherapy but also by
systemic chemotherapy. Vincritine is associated with peripheral neuropathies, and its
intrathecal administration results in infatal neurotoxicity. Capecitabine, oxaliplatin and
paclitaxel cause sensory neuropathy. Peripheral neuropathy with ototoxicity is a dose limiting
toxicity of cisplatin. Cytarabine and 5-fluorouracil causes cerebellar toxicity manifested by
ataxia, and loss of coordination between eyes and hands. Arachnoditis may result with
intrathecal administration of cytarabine and methotrexate.

1.14.16.5 Renal Toxicity

Nephrotoxicity or (renal toxicity) is associated with methotrexate, coplation,
and. Ifosfamide. Amifostine may be used to protect the kidneys from the nephrototoxic effects of
cisplatin.

1.14.16.6 Hepatotoxicity

Asparaginase, thioguanine, cytarabine, methorexate and mercaptopurine are
known to cause hepatotoxicity that is manifested as jaundice, hepatitis and elevation in liver
transemise enzymes.

1.14.16.7 Cardiotoxicity

Anticancer drugs that are associated with chronic cardiotoxicity (such as
precipitation of congestive heart failure) are daunorubicin, doxorubicin, epirubician,
idarubicin and mitoxantrone, trastuzumab and bevacizumab. Dexrazoxane is a
cardioprotectant that can be used with daunorubicin (doxorubicin) to minimize their
cardiotoxicity.

1.14.16.8 Pulmonary Toxicity

Chemotherapeutic agents associated with pulmonary toxicity (pulmonary
fibrosis, short ness of breath, cough and low grade fever) include bleomycin, melphlan,
chlorambucil, busulfan, carmustine and mitomtcin. Erlotinib produces interstitial lung
diseases; pharyngo-laryngeal dysaesthesia while bevacizumab leads to pulmonary haemorrhage (Sharma 2008).

1.14.16.9 Infertility Toxicity

Large amount of alkylating agents like thiotepa, mechloretamine, chlorambucil and melphalan and cylophosphamide as well as procarbazine are associated with significant incidence of infertility in males as well as females which may be temporary or even permanent.

1.14.16.10 Hypersensitivity Reactions

Skin rash is most common with retinoids, cetuxmab and procarbazine. Fever and chill are common associated with cytarabine, oprelvekin and monoclonal antibodies. Life threatening hypersensitivity reaction, including anaphylaxis, appears to be most common with carboplatin, etoposide, cisplatin and paclitaxel.

1.14.17 Clinical uses and Adverse Effects of Anticancer Drugs

Anticancer drugs are having adverse effects when it is used in the chemotherapy treatment of cancer (Sharma 2008). Anticancer drugs with their adverse effects and clinical uses are shown in the following Table 18.
### Table 18. Clinical uses and Adverse Effects of Anticancer Drugs

<table>
<thead>
<tr>
<th>SI.No</th>
<th>Anticancer drugs</th>
<th>Clinical Uses</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Alkylating Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Busulfan</td>
<td>Polycythemic vera, chronic myelocytic</td>
<td>Cataract formation, gynaecomastia, dermatologic toxicity, myelosuppression, pulmonary toxicity.</td>
</tr>
<tr>
<td>2.</td>
<td>Nitrosoureas (Carmustine)</td>
<td>Colorectal cancer, multiple myeloma, Hodgkin&quot;s diseases, CNS tumours, lymphoma, melanoma.</td>
<td>GIT toxicity, myelosuppression, hepatotoxicity, pulmonary fibrosis.</td>
</tr>
<tr>
<td>3.</td>
<td>Semustine</td>
<td>Multiple myeloma, lymphoma, Colorectal cancer, melanoma, CNS tumours, Hodgkin&quot;s diseases</td>
<td>Pulmonary fibrosis, myelosuppression, GIT toxicity, hepatotoxicity</td>
</tr>
<tr>
<td>4.</td>
<td>Lomustine</td>
<td>Melanoma, Hodgkin&quot;s diseases, colorectal cancer, Multiple myeloma, CNS tumours, lymphoma,</td>
<td>Hepatotoxicity, Pulmonary fibrosis, GIT toxicity, myelosuppression,</td>
</tr>
<tr>
<td>5.</td>
<td>Cyclophosphamide</td>
<td>Prostrate and ovarian cancer, Hodgkin&quot;s disease, testicular cancer, breast cancer, lung cancer, multiple</td>
<td>Hepatotoxicity, SIADH, alopecia, Immuno suppression, myelosuppression, nausea, stomatitis, haemorrhagic cystitis,</td>
</tr>
<tr>
<td></td>
<td>Drug</td>
<td>Indications</td>
<td>Side Effects</td>
</tr>
<tr>
<td>---</td>
<td>----------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>6.</td>
<td>Chlorambucil</td>
<td>Myeloma, Hodgkin’s disease, lymphoma, lymphosarcoma, chronic lymphocytic leukemia, ovarian cancer</td>
<td>Nausea, pulmonary fibrosis, myelosuppression, hepatotoxicity, vomiting, dermatotoxicity</td>
</tr>
<tr>
<td>7.</td>
<td>Dacarbazine</td>
<td>Hodgkin's disease, melanoma, sarcoma</td>
<td>Dermatotoxicity, hepatotoxicity, alopecia, myelosuppression, nausea, fever</td>
</tr>
<tr>
<td>8.</td>
<td>Melphalan</td>
<td>Breast cancer, multiple myeloma, ovarian carcinoma</td>
<td>SIADH, teratogenicity, dermatotoxicity, pulmonary fibrosis, GIT distress, myelosuppression</td>
</tr>
<tr>
<td>9.</td>
<td>Ifosfamide</td>
<td>Ovarian and testicular carcinoma, multiple myeloma, sarcoma</td>
<td>Vomiting, nausea, myelosuppression, lethargy, confusion, haemorrhagic cystitis</td>
</tr>
<tr>
<td>10.</td>
<td>Mechlorethamine</td>
<td>Lymphoma, Hodgkin’s disease</td>
<td>Tissue necrosis, alopecia, nausea, neurotoxicity, myelosuppression</td>
</tr>
<tr>
<td>11.</td>
<td>Thiotepa</td>
<td>Rhabdomyosarcoma, lymphomas, ovarian, breast cancer</td>
<td>Infertility, vomiting, nausea, dermatotoxicity, myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>12.</td>
<td>Streptozocin</td>
<td>Pancreas (islets cell carcinoma)</td>
<td>Myelosuppression, hepatotoxicity, fever, nausea, hypoglycemia</td>
</tr>
<tr>
<td>13.</td>
<td>Temozolomide</td>
<td>Melanoma, brain tumour</td>
<td>Upper abdominal distress, myelosuppression</td>
</tr>
<tr>
<td>14.</td>
<td>Estramustine</td>
<td>Carcinoma of prostrate</td>
<td>Thromophlebitis, cardiotoxicity, nausea, gynaecomastia</td>
</tr>
</tbody>
</table>

### Antimetabolites

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>15.</td>
<td>Methotrexate (Folic acid analogues)</td>
<td>Rheumatoid arthritis, psoriasis, acute lymphoblastic leukemia, Choriocarcinoma; head, neck, breast, cervical, lung carcinoma</td>
<td>GIT toxicity (diarrhoea and ulcerative mucositis), myelosuppression, neurotoxicity, hepatotoxicity (with prolonged use) nephrotoxicity, alopecia</td>
</tr>
<tr>
<td>16.</td>
<td>Purine analogues Mercaptopurine</td>
<td>Myelogenous leukemia (chronic and acute)</td>
<td>Stomatitis, mild nausea, hepatotoxicity, myelosuppression</td>
</tr>
<tr>
<td>17.</td>
<td>Thioguanine</td>
<td>Myelogenous leukemia (acute and chronic)</td>
<td>Hepatotoxicity (less common compared to mercaptopurine) myelosuppression, mild nausea</td>
</tr>
<tr>
<td>18.</td>
<td>Fludarabine</td>
<td>Lymphocytic leukemia (chronic)</td>
<td>Stomatitis, alopecia, mild nausea, myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>19.</td>
<td>Cladribine</td>
<td>Leukemia (hairy cell)</td>
<td>Nausea, skin rash, nephrotoxicity, myelosuppression</td>
</tr>
<tr>
<td>20.</td>
<td>Pentostatin</td>
<td>Hairy cell leukemia</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>21.</td>
<td>Pyrimidine analogues</td>
<td>Lymphoma, myelogenous leukemia (acute and chronic)</td>
<td>Stomatitis, neurotoxicity, nausea, conjunctivitis, myelosuppression</td>
</tr>
<tr>
<td>22.</td>
<td>Capecitabine</td>
<td>Metastatic breast cancer, colorectal cancer</td>
<td>Hepatotoxicity, vomiting, skin rash, nausea, myelosuppression</td>
</tr>
<tr>
<td>23.</td>
<td>Flurouracil</td>
<td>Superficial basal cell carcinoma, lung, ovary, breast, cervix, prostrate, bladder, head and neck carcinoma, GIT adenocarcinoma</td>
<td>Stomatitis, photosensitivity, neurotoxicity (cerebellar ataxia), alopecia</td>
</tr>
<tr>
<td>24.</td>
<td>Gemcitabine</td>
<td>Pancreatic adenocarcinoma</td>
<td>Flu-like symptoms, myelosuppression</td>
</tr>
<tr>
<td>25.</td>
<td>Floxuridine</td>
<td>Cancer of cervix, breast</td>
<td>Mild myelosuppression</td>
</tr>
<tr>
<td>No.</td>
<td>Chemotherapy</td>
<td>Tumours/Tissues Affected</td>
<td>Toxicities</td>
</tr>
<tr>
<td>-----</td>
<td>--------------</td>
<td>--------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>26.</td>
<td>Antibiotics</td>
<td>Bleomycin</td>
<td>Ovary, bladder, prostate, lung, head and neck, superficial basal cell carcinoma, GIT adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-Hodgkin's and Hodgkin's lymphomas, testicular carcinoma, squamous cell carcinoma of neck, cervix, skin and head</td>
<td>Nausea, vomiting, skin rash, pulmonary toxicity, fever</td>
</tr>
<tr>
<td>27.</td>
<td>Mitomycin</td>
<td>Carcinoma of Pancreas, colon, head, neck, breast, stomach, and lung</td>
<td>Tissue necrosis, stomatitis, hepatotoxicity, alopecia, pulmonary toxicity, myelosuppression</td>
</tr>
<tr>
<td>28.</td>
<td>Actinomycin-D</td>
<td>(dactinomycin) Neuroblastoma, chorio carcinoma, rhabdomyosarcoma, testicular sarcoma, Edwig's sarcoma, Wilm's tumour</td>
<td>Stomatitis, mucositis, tissue necrosis, vomiting, nausea, myelosuppression</td>
</tr>
<tr>
<td>29.</td>
<td>Daunorubicin</td>
<td>Leukemia (acute myelocytic)</td>
<td>Alopecia, tissue necrosis, cardiotoxicity, myelosuppression, stomatitis</td>
</tr>
<tr>
<td>30.</td>
<td>Doxorubicin</td>
<td>Multiple myeloma, Wilm's tumour, acute leukemia, thyroid, breast, ovarian, endometrial, bladder cancer, Hodgkin's disease</td>
<td>Radiation recall reaction, cardiotoxicity, stomatitis, myelosuppression, tissue necrosis, Alopecia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Natural Products**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vinblastine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38.</td>
<td>Vinorelbine</td>
<td>Non- small cell lung cancer, lung, bald cancer, Kaposi’s</td>
<td>Lesser neruo-toxicity, dermatitis, anorexia,</td>
</tr>
</tbody>
</table>
### Camptothecins

- **Topotecan**
  - Colon, ovarian, small cell lung cancer and lung cancer.
  - Flu-like symptoms, myelosuppression, vomiting

### Irinotecan

- Small cell lung cancer, lung cancer Colon and ovarian cancer
  - Myelosuppression, vomiting, nausea, flu-like symptoms

### Enzymes

- **L-Asparaginase**
  - Lymphoma, leukaemia, acute lymphocytic
  - Fever, hepatotoxicity, allergic reactions, nausea, hair and GIT follicles.

### Taxanes

- **Docetaxel**
  - Neck and breast cancer, ovarian and lung carcinoma
  - Alopecia, hypersensitivity, Myelosuppression, bradycardia, neuropathy

- **Paclitaxel**
  - Lung carcinoma, breast cancer, neck and lung cancer.
  - Hypersensitivity, bradycardia, myelosuppression, neuropathy, Alopecia

### Miscellaneous Agents

- **Hydroyurea (HU)**
  - Sickle cell anaemia, polycythaemia vera, chronic myelogenous cancer,
  - Alopecia, skin reactions, hyperpigmentation,

- **Procarbazine**
  - Hodgkin's disease, lymphoma, multiple myeloma, brain tumors
  - Myelosuppression, nausea, vomiting, skin rash,
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>chromosomal damage, disulfiram type reaction with ethanol</td>
<td></td>
</tr>
<tr>
<td>46.</td>
<td>Oxaliplatin</td>
<td>Colorectal cancer</td>
<td>Pharyngo-laryngael dysaesthesia, paraesthesias, diarrhoea, myelosuppression (less)</td>
</tr>
<tr>
<td>47.</td>
<td>Arsenic trioxide</td>
<td>Acute Promyelocytic Leukaemia (APL)</td>
<td>Syndrome like retinoic acid, cardiotoxicity, dermatotoxicity, vomiting, nausea</td>
</tr>
<tr>
<td>48.</td>
<td>Hexamethyl melamine (HMM) or Altretamine</td>
<td>Ovarian cancer</td>
<td>Nausea, vomiting, myelosuppression, neurotoxicity (rare)</td>
</tr>
<tr>
<td>49.</td>
<td>Cisplatin</td>
<td>Testicular cancer, neck and lung cancer, prostrate and bladder cancer</td>
<td>Vomiting, nausea, hearing loss, nephrotoxicity, allergic reactions.</td>
</tr>
<tr>
<td>50.</td>
<td>Carboplatin</td>
<td>Neck and lung, testicular cancer, cancer, bladder cancer and prostrate</td>
<td>Other toxicities less than cisplatin myelosuppression,</td>
</tr>
<tr>
<td>51.</td>
<td>Thalidomide</td>
<td>AIDS related cachexia, graft versus host disease, melanoma, multiple myeloma</td>
<td>Nephrotoxicity, teratogenic effects, neurotoxicity, tong discolouration, taste alteration</td>
</tr>
<tr>
<td>53.</td>
<td>Epidermal Growth Factors Receptor</td>
<td>Metastaric non small cell lung cancer and other solid tumours</td>
<td>Anorexia, diarrhoea, acneiform skin rash</td>
</tr>
</tbody>
</table>

*Department of Pharmacy, JJT University, Rajasthan*
<table>
<thead>
<tr>
<th>No.</th>
<th>Drug Name</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>Erilotinib</td>
<td>Metastatic non small cell lung cancer and other solid tumours</td>
<td>Acneiform skin rash, Anorexia, diarrhea</td>
</tr>
<tr>
<td>55</td>
<td>Protosome Inhibitors Bortezomib</td>
<td>Refactory and relapsed multiple myeloma</td>
<td>Bone marrow suppression, fatigue, diarrhea, peripheral neuropathy</td>
</tr>
<tr>
<td>56</td>
<td>Estrogen receptor antagonist</td>
<td>Male breast carcinoma, breast carcinoma,</td>
<td>Hot flushes, deep vein thrombosis, oedema</td>
</tr>
<tr>
<td>57</td>
<td>Toremifen</td>
<td>Breast carcinoma, male breast carcinoma</td>
<td>Deep vein thrombosis, hot flushes, oedema, endometrial hyperplasia</td>
</tr>
<tr>
<td>58</td>
<td>Aromatase Inhibitors Letrozole</td>
<td>Postmenopausal breast cancer in women</td>
<td>Hot flushes arthragias, mild nausea and headache.</td>
</tr>
<tr>
<td>59</td>
<td>Anastrozole</td>
<td>ER-positive metastatic breast cancer in postmenopausal women that are resistant to tamoxifen therapy</td>
<td>Mild nausea, headache, hot flushes and arthragias.</td>
</tr>
<tr>
<td>61</td>
<td>Rituximab</td>
<td>Chronic lymphocytic leukaemia, B-cell lymphoma</td>
<td>Infusion related hypersensitivity, like rashes.</td>
</tr>
<tr>
<td>62</td>
<td>Trastuzumab</td>
<td>Breast cancer</td>
<td>GIT enterotoxicity, cardiomyopathy, infusion</td>
</tr>
<tr>
<td>Table</td>
<td>Drug</td>
<td>Cancer Type</td>
<td>Side Effects</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td>63</td>
<td>Cetuximab</td>
<td>Colorectal cancer, non small cell lung cancer, breast and pancreatic cancer</td>
<td>Infusion related toxicity, skin rash (70-75 %)</td>
</tr>
<tr>
<td>64</td>
<td>Bevacizumab</td>
<td>Metastatic colorectal cancer with 5-FU, breast cancer and renal cell cancer.</td>
<td>Mild neuteropenia, hypertension, risk of congestive cardiac failure, proteinuria and pulmonary haemorrhage.</td>
</tr>
<tr>
<td>65.</td>
<td>Protectants Filgrastim</td>
<td>To prevent chemotherapy - induced neuteropenia, to increases neutrophil counts and to prevent infections.</td>
<td>Myalgia, bone pain and pericardial effusions</td>
</tr>
<tr>
<td>66</td>
<td>Amifostine</td>
<td>Adminstrated before cisplatin to reduce incidence of nephrotoxicity and before radition therapy for neck and head to reduce xerostomia.</td>
<td>Nausea, vomiting and hypertension.</td>
</tr>
<tr>
<td>67</td>
<td>Mesna</td>
<td>Co-administrated with cyclophosphamide or ifosfamide to prvent haemorrhagic cystitis</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>68</td>
<td>Dexrazoxane</td>
<td>Coadministrated with doxorubicin in patients of breast carcinoma to reduce the incidence of cardiomyopathy</td>
<td>Myelosuppression, alteration in renal and liver function test results</td>
</tr>
<tr>
<td>69</td>
<td>Saragramostim</td>
<td>To prevent chemotherapy -</td>
<td>Myalgia, bone pain,</td>
</tr>
</tbody>
</table>
### Introduction

<table>
<thead>
<tr>
<th>No.</th>
<th>Drug</th>
<th>Action</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>Oprelvekin</td>
<td>To prevent chemotherapy induced thrombocytopenia</td>
<td>Pericardial effusions, peripheral oedema, palpitations, dyspnoea, myalgia, fatigue, arthralgia</td>
</tr>
<tr>
<td>71</td>
<td>Thrombopoietin</td>
<td>To prevent chemotherapy induced thrombocytopenia</td>
<td>Formation of antirecombinant thrombopoietin antibodies (immunogenicity) which subsequently negates the benefits</td>
</tr>
<tr>
<td>72</td>
<td>Levamisole</td>
<td>Combined with 5-FU to improve survival of patients of colorectal cancer</td>
<td>Flu-like symptoms, vomiting and nausea</td>
</tr>
<tr>
<td>73</td>
<td>Hormones and Antagonists Cetrorelix</td>
<td>Prostatic carcinoma</td>
<td>Less toxic than Gn-RH agonists; pain and swelling at the injection</td>
</tr>
<tr>
<td>74</td>
<td>Somatostatin analogues Octreotide</td>
<td>To inhibit secretions of various autacoids from metastatic carcinoid tumour and peptide hormone from islet cell carcinoma</td>
<td>Gall bladder stone, Vit B&lt;sub&gt;12&lt;/sub&gt; deficiency, abdominal pain, nausea.</td>
</tr>
<tr>
<td>75</td>
<td>Goserelin</td>
<td>To treat prostatic carcinoma and estrogen receptor positive, breast</td>
<td>Headache, allergic manifestations, nausea.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>76.</td>
<td>Buserelin</td>
<td>Breast cancer, ovarian cancer, to treat prostatic carcinoma and estrogen receptor positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allergic manifestations, headache, nausea.</td>
<td></td>
</tr>
<tr>
<td>77.</td>
<td>Leuprolide</td>
<td>Breast and ovarian cancer, It will activate testicular or ovarian functions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allergic manifestations, headache, nausea</td>
<td></td>
</tr>
<tr>
<td>78.</td>
<td>Ganirelix</td>
<td>Prostatic carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less toxic than Gn-RH agonists; pain and swelling at the injection</td>
<td></td>
</tr>
<tr>
<td>79.</td>
<td>Abarelix</td>
<td>Prostatic carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain and swelling at the injection, less toxic than Gn-RH agonists</td>
<td></td>
</tr>
<tr>
<td>80.</td>
<td>Prednisolone</td>
<td>Multiple myeloma, breast cancer, cancer related hypercalcaemia, multiple myeloma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peptic ulcer, hypokalaemia, fluid retention, diabetes, muscle wasting, susceptibility to infections</td>
<td></td>
</tr>
<tr>
<td>81.</td>
<td>Dexamethasone</td>
<td>Breast cancer, cancer related hypercalcaemia, multiple myeloma, multiple myeloma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypokalaemia, fluid retention, diabetes, peptic ulcer, muscle wasting, susceptibility to infections</td>
<td></td>
</tr>
<tr>
<td>82.</td>
<td>Aminoglutethimide</td>
<td>Used for Cushing&quot;syndrome associated with adrenal carcinoma, Carcena of breast, adrenal and prostate cancer.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lethargy, rashes, ataxia, hypotension, dizziness, myelosuppression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug</td>
<td>Indications</td>
<td>Adverse Effects</td>
</tr>
<tr>
<td>---</td>
<td>--------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>83</td>
<td>Trilostane</td>
<td>Carcinoma of breast, adrenal and prostrate cancer, Cushing syndrome associated with adrenal carcinoma,</td>
<td>Ataxia, hypotension, dizziness, myelosuppression, lethargy, rashes</td>
</tr>
<tr>
<td>84</td>
<td>Exemestane</td>
<td>ER-positive metastatic breast cancer in postmenopausal women that are resistant to tamoxifen therapy</td>
<td>Mild nausea, headache, hot flushes and arthragias.</td>
</tr>
<tr>
<td>85</td>
<td>Fluvestrant</td>
<td>Breast carcinoma, male breast carcinoma</td>
<td>Deep vein thrombosis, hot flushes, oedema, endometrial hyperplasia</td>
</tr>
<tr>
<td>86</td>
<td>Flutamide (Androgen receptor blockers)</td>
<td>Prostate carcinoma</td>
<td>Nausea, mild gynaecomastia, transient elevation of liver enzymes</td>
</tr>
<tr>
<td>87</td>
<td>Bicalutamide</td>
<td>It is have a longer plasma half lives that allows once daily oral dosing as compared to flutamide which needs thrice daily dose schedule, prostate carcinoma</td>
<td>Hot flushes, nausea, mild gynaecomastia, transient elevation of liver enzymes</td>
</tr>
<tr>
<td>88</td>
<td>Nilutamide</td>
<td>Prostate carcinoma nilutamide have a longer plasma half lives that allows once daily oral dosing as compared to flutamide which needs thrice daily dose schedule</td>
<td>Transient elevation of liver enzymes, hot flushes, nausea and mild gynaecomastia</td>
</tr>
<tr>
<td>89</td>
<td>Hydroxyprogesterone</td>
<td>Breast carcinoma and metastatic endometrial cancer</td>
<td>Acne, hirsutism, neurotoxicity.</td>
</tr>
</tbody>
</table>
### Introduction

<table>
<thead>
<tr>
<th>90</th>
<th>Medroxyprogesterone</th>
<th>Metastaic endometrial cancer and breast carcinoma</th>
<th>Neurotoxicity, acne, hirsutism</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td>Megestrol acetate</td>
<td>Breast carcinoma and metastaic endometrial cancer</td>
<td>Hirsutism neurotoxicity, acne</td>
</tr>
</tbody>
</table>

#### 1.14.18 Nursing Care and Consideration during the Administration of Anti-Neoplastic

#### 1.14.18.1 General

**1.14.18.1.1 Assessment to be performed includes:**

- Weekly blood analysis, Complete Blood count (CBC), platelet and differential count should be taken. If the platelet count is less than 75,000/mm$^3$ or the WBC count is $<4000$/mm$^3$, drug should be withheld and the prescriber should be informed.

- Renal function studies should be performed before and during the therapy. The tests should include Blood Urea Nitrogen (BUN), creatinine, urine C$_{Cr}$ (Urine creatinine clearance) and serum uric acid.

- Maintain strict intake output chart, decreased urine output (i.e. less than 30ml/hr) should be notified to the concerned personnel.

- Monitor vital signs every fourth hourly.

- Before and during the therapy liver function tests (LDH, ALT, bilirubin, AST) should be conducted monthly or as needed.

- Assess the patient regularly for any signs and symptoms of haemorrhage. (Including bruising, guaiac, haematuria, petechiae etc.)

- Assess the patient for signs and symptoms of jaundice (yellowish discolouration of sclera and skin, dark urine) and other GI symptoms clay coloured stools, abdominal pain, diarrhoea and fever.

- Check for any edema in feet, joint pain, stomach pain, breaks in skin and inflammation in mucosa.

#### 1.14.18.2 Care to be taken while administering the drug

- Evaluate the IV site for any abnormalities, keep the site clean, regularly change the site, and follow sterile technique while administering the drug.
- Protective isolation should be provided if and when the WBC count is low.
- Provide comprehensive oral care; avoid use of hard bristle brush.

### 1.14.18.1.3 Educate the patient and family

- Explain the patient various signs of infection (increased temperature, malaise, sore throat)
- Teach the signs of anemia including fatigue, faintness, shortness of breath, headache, and irritability.
- To avoid the use of commercial mouthwash and razors.
- The patient and family should be advised to report any abnormalities seen during and after the treatment.

### 1.14.18.4 Care specific to each drug

#### Alkylating agent

1. **Busulfan**
   - Check bone marrow status prior to chemo-therapy.
   - Withhold the drug if the platelet count or the WBC count is less than 150000/mm$^3$ or 15000/mm$^3$ respectively.
   - Chest x-ray should be taken twice weekly during the duration of treatment.
   - Monitor renal parameters: serum uric acid, urine CCr and BUN before and during the therapy.
   - To prevent urate deposit and calculi formation, increase fluid intake to 2 to 3 litres per day.

   **Teach the patient to**
   - Avoid usage of products containing ibuprofen or aspirin, commercial mouthwash and razors.
   - Report symptoms of haemorrhage.
   - Inform signs of faintness, jaundice, signs of sepsis, headache.

2. **Carboplatin**
   - Assess the platelet count, CBC (differential) once a week.
If the platelet count is <100,000mm$^3$ or the neutrophil count is <2000/mm$^3$ withhold the drug.

Maintain I/O chart. Report if urine output is less than 30 ml/hr.

Before and during the study monitor renal parameters.

Asses for signs and symptoms of jaundice.

Administer an anti-emetic 30 to 60 min prior to giving the drug.

Check for anaphylactic reactions after drug administration.

**Patient teaching**

- To avoid breastfeeding during the treatment.
- Impotence or amenorrhea during the treatment is reversible after the treatment is discontinued.
- Advice fertile patients to use contraception.
- Advice the patient to avoid over the counter drugs, the use of sharps.
- Avoid the crowds and potential sources of infection.

3. **Carmustines**

- Evaluate the hepatic and renal parameters.
- Weekly assess the CBC count and platelet count. If platelet is < 1 lakh or WBC is < 4 thousand notify the prescriber.
- Before and during the therapy perform pulmonary function tests. Chest films should be obtained twice weekly during the therapy.
- Assess for signs and symptoms respiratory distress.
- Monitor urine output.
- Report any incidence of bleeding (haematuria, guaiac, bruising, petechiae, mucosal) 8 hourly
- In case of anaemia, transfuse blood or RBC colony stimulating factors.
- Avoid IM injections if platelet count is low i.e. less than 1 lakh.

**Patient education**

- Report any signs of respiratory distress.
Introduction

- Perform daily oral examinations and report to the care giver if there is any abnormality (bleeding, white spots, ulcerations etc.)
- Avoid the use of NSAIDs, commercial mouth wash and razors.
- In case of stomatitis avoid intake of food containing citric acid
- Advice the patient to report the signs and symptoms of anaemia and infection.
- Patient should avoid vaccinations, withhold breast feeding should be avoided during the treatment.
- If fertile use contraception during treatment

4. Lomustine
- Assess renal, hepatic and pulmonary function before and during the therapy.
- Obtain chest films twice weekly during the treatment span.
- Monitor vitals q4h
- Check for signs and symptoms of bleeding, respiratory distress, jaundice, and inflammation.
- Check for any abnormalities at the site of injection.
- Administer antibiotics as a prophylaxis of infection

Teach the patient and family
- About protective isolation.
- To avoid any food that can cause buccal irritation (citrus, hot or food with rough texture)
- Withhold breast feeding, if the patient is fertile use effective contraception.
- Avoid commercial mouthwash, over the counter drugs razors etc.
- Report any signs of respiratory distress, infection, and anemia.

5. Chlorambucil
- Assess for signs and symptoms of jaundice, respiratory abnormalities and bleeding.
- Evaluate platelet and CBC count weekly, withhold the drug if WBC count is less than 2 thousand or granulocyte count is $<$1000/mm$^3$.
- Perform hepatic studies, renal studies and pulmonary function test, before and during the therapy (chest X-ray should be taken twice weekly).
• Maintain strict I/O chart and report decreased urine output (i.e. less than 30ml/hr)
• Administer all drugs per orally, avoid parental administration of drugs.
• Monitor vital signs 4th hourly.
• Patient education
  • Teach the patient to identify the signs of infection, anemia, bleeding.
  • Advice the patient to report the signs of infection, bleeding and anemia.
• Avoid usage of NSAIDs esp. ibuprofen and aspirin
• Avoid breastfeeding; therapy may lead to irreversible gonadal suppression. Use contraception during the treatment and post therapy for several months.
• Increase the fluid intake to 2-3 litres per day unless otherwise indicated. Report any decrease in urine output.

6. Cyclophosphamide
• Assess the patient for haemorrhagic cystitis; maintain strict intake output chart. Report if urine output is less than 1 ml/kg body wt/hour. Renal studies (blood urea nitrogen, urine creatinine clearance, and serum uric acid) should be performed before and during the test.
• Complete blood count, differential platelet count should be checked weekly. Hold back the drug if the WBC count is less than 2500 or the platelets count is below 75,000.
• Respiratory functions should be evaluated (chest X-ray, pulmonary function tests should be taken before and during the treatment). Auscultate the chest for abnormal breath sounds. Dry cough, dyspnoea, tachypnea, chest pain should be reported.
• Check vitals q2h.
• Hepatic studies should be conducted monthly. Watch for signs and symptoms of jaundice (yellowish discoloration of the skin, sclera, dark urine, abdominal pain, diarrhoea, clay colored stools, fever etc.).
• Oral mucosa should be regularly checked for white patches soreness ulceration, pain, bleeding etc.
• Administer the drug in the morning so that it can be eliminated before night.
- Antacid and antiemetic should be administered as needed.

**Instruct the patient and family**

- About the importance of protective isolation and prevention of infection.
- To avoid food causing gastric and oral irritation (citric, hot, spicy etc)
- Regarding signs of anemia and to report if present (irritability, fatigue, shortness of breath etc)
- Patient should report any incidence of bleeding and respiratory distress.
- Avoid vaccinations, ibuprofen and aspirin products during therapy.

7. **Cisplatin**

- Weekly assessment of complete blood count, platelet count (withhold the drug if the WBC count drops below 4,000 or platelet count below 100,000)
- Renal and hepatic studies should be conducted periodically (do not administer the drug if blood urea nitrogen <25 mg/dl, creatinine <1.5 mg/dl)
- Watch out for signs and symptoms of jaundice, edema and out of urine is very low (oliguria).
- Provide regular oral care; avoid intramuscular injection if platelet count is less than 1 lakh.
- Fluid intake should be increased to prevent the formation of calculi and urate deposits

**Patient education**

- Advice the care giver to report the signs of infection (pyrexia, sore throat, malaise etc.), anemia (headache, tiredness, dyspnoea), bruising, bleeding, petechiae, loss of sensation in the extremities, flank pain, decreased urine output, joint pain, edema etc.
- Avoid use of NSAID’s, ibuprofen, aspirin and foods that cause oral and gastric irritation.
- Impotence or amenorrhea developed during the treatment is reversible after the treatment.
- Patient should not receive any vaccination during the treatment.
8. **Dacarbazine**
   - Drug administration should be discontinued if the WBC is less than 4000 or platelet is less than 75 thousand.
   - Teach the patient and care giver signs and symptoms of complication and anaphylactic reaction (fever, jaundice, bleeding and inflammation)
   - Administer antibiotics as per prescription to avoid infection, anti-emetics should be provided if the patient complaints of nausea and vomiting
   - Follow strict medical asepsis, increase fluid intake to prevent renal complication.
   - In case of inflammation at the site of injection provide hot compress.

**Teach patient and care giver**
- Use sunscreen while going out and avoid prolonged exposure to sun
- Wear a hair piece in case of severe hair loss.
- Report any abnormality or discomfort.
- Aspirin and ibuprofen should be avoided.
- Use contraceptives, avoid breast feeding and vaccination during the treatment and after the treatment for several months

9. **Melphalan**
   - Discontinue the drug if the WBC count is<3000mm$^3$ or platelet count is < 1 lakh.
   - Check blood urea nitrogen, urine creatinine and serum uric acid regularly during and after the therapy.
   - Evaluate for signs and symptoms of infection, haemorrhage and jaundice.
   - Check buccal cavity every 8 hourly for dryness, ulceration, oral pain, sores, bleeding and dysphagia.
   - Injection site should be checked for local irritation, pain, discoloration and burning.
   - Follow strict aseptic techniques while giving patient care. Increase the intake of fluids to 2-3 litres per day.
   - Provide low purine diet: dried beans, peas, and organ meat (kidney, liver) to maintain alkaline urine.
   - If the injection site develops inflammation, provide hot compress.
Teaching points

• Sterility and amenorrhea developed during the treatment is reversible upon discontinuing the treatment.

• Food containing citric acid, rough texture etc. should be avoided to prevent buccal irritation.

• Report any bleeding, signs of infection, suspected pregnancy, signs of anemia and signs of jaundice.

• Usage of aspirin products, NSAID”s, alcohol should be avoided.

10. Mechlorethamine

• Hold out drug administration if platelet count is less than 75 thousand and the WBC count is less than thousand per mm$^3$.

• Temperature should be appraised every fourth hour rectal temperature should not be checked.

• During the therapy renal function test and hepatic studies should be conducted frequently as suggested by the physician.

• Watch out for symptoms of anaphylactic reaction (rash, urticaria, flushing, pruritus, skin lesions, itching) and bleeding.

• The drug should be stored at room temperature in dry form.

• In order to maintain alkalinity of urine, provide diet low in purine.

Teaching points

• Enlighten the importance of protective isolation

• Teach the patient signs and symptoms of jaundice, infection, anaphylactic reaction and bleeding.

• Advice the patient to inform its occurrence to the concerned health professional.

• Avoid the use of razors and commercial mouthwash.

• Advice the patient to examine mouth daily. Watch for bleeding, white spots and ulceration.

Antimetabolites

11. Capecitabine
• Blood investigations (RBC, haematocrit, hgb, platelet count,) should be conducted daily. If the WBC count is less than 4000/mm$^3$ or the platelet cont is less than 75,000/mm$^3$ or if the Hgb, Hct or RBC count is low, prescriber should be notified.
• Renal and hepatic parameters should be evaluated periodically or as required.
• Check vital signs q4h, record and report any abnormalities.
• Assess for signs and symptoms of respiratory distress (crackles, tachypnea, chest pain, and dry cough), pallor, lethargy, personality changes accompanying high doses.

Teach
• Signs and symptoms of Palmar plantar erythrodysesthesia (hand and foot syndrome) which includes swelling, erythema and blistering of extremities with or without pain, paraesthesia and tingling sensation.
• Pregnancy and breast feeding should be avoided while on treatment.
• Avoid oral intake of mucosal irritants, take water within 30mints of food intake.
• Report any abnormalities (signs and symptoms of infection, anemia,or haemorrhage)

12. Decitabine
• Weekly appraisal of Complete blood count. Withhold the drug if granulocyte count is less than 750/mm$^3$
• Bilirubin, AST (aspartate-aminotransferase), ALT (alanine-aminotransferase) and alkaline phosphatase baseline should be obtained before each dose.
• Renal parameters should be evaluated before each dose. Monitor vital signs for signs and symptoms of infection.
• Maintain strict intake output (I/O) chart. Report if the urine output decreases to less than 30 ml/hr.
• Do thorough cardiac assessment including chest x-ray radio-nuclide angiography, electrocardiography; watch for low QRST and ST- segment variation, dysrhythmias (heart block, sinus tachycardia).
• Assess the patient for signs of congestive heart failure (jugular vein distension, crackles, weight gain, edema etc.)
Assess for signs of dehydration loss of skin turgor, decreased urine output, weakness, dry skin, restlessness.

Inspect the oral cavity for any abnormalities, look out for GI symptoms

Increase intake of fluids to 2-3 litres a day to prevent complication.

Teach the patient

Advice the patient and relative to report any abnormalities or discomfort experienced during the treatment (infection, bleeding, fatigue, dyspnea, etc.)

Contraceptives should be taken while on treatment, pregnancy and breast feeding should be avoided.

Inform that the urine and other body fluid may be red-orange in colour for 48 hours.

Avoid crowds and potential sources of infection. Do not take vaccines while on treatment.

13. Cytarabine

Check CBC (complete blood count) and platelet count weekly. If the CBC (RBC (red blood cells), haemoglobin and haematocrit) is low, platelet count is <50,000/mm$^3$, or WBC count is <1000/mm$^3$ then withhold the drug.

Regularly evaluate hepatic and renal parameters, any deviation from normal should be reported.

Observe for signs and symptoms of anaphylaxis (respiratory distress, pruritus, facial edema, rash). Fully equipped resuscitation trolley should be kept nearby.

Monitor the patient for dehydration, GI symptoms, local irritation at the infection site, bleeding, hematuria, mouth ulcers, and oral dryness.

Closely monitor for signs and symptoms of chemical arachnoiditis (nausea, headache, vomiting, neck rigidity, fever and meningism), cerebro-spinal fluid pleocytosis: may be decreased by dexamethasone administration.

Detect signs of pulmonary edema (crackles, chest pain, unproductive cough, tachypnea, fatigue, increased pulse, lethargy and pallor). Pulmonary edema may prove fatal on rare occasion.
• Administer allopurinol to maintain alkalisation of urine and uric acid levels. Provide low purine diet.

**Teach family and patient**

• Report signs of respiratory distress, stomatitis (bleeding, white spots, ulceration in the mouth), anemia (headache, fatigue, shortness of breath, faintness), bleeding.

• Increase fluid intake to 3 litres per day to avoid renal complication.

• Use reliable contraception during the treatment and up to 4 months after treatment completion.

14. *Etoposide*

• Hold back the drug if white blood cells count is < 1000 or platelet count is < 50,000.

• Check blood urea nitrogen, urine creatinine clearance, serum uric acid, electrolytes, bilirubin, aspartate-aminotransferase, alanine – aminotransferase, before and during the treatment.

• Monitor blood pressure every 15 mints, if the systolic blood pressure drops below 90 mm of Hg, discontinue the drug and inform the prescriber.

• Teach the patient symptoms indicating severe allergic reaction and to report its occurrences.

• Check for signs of dehydration (decreased urine output, poor skin turgor, restlessness, rapid respirations, dry skin, weakness, restlessness).

**Teach**

• Increase fluid intake up to 3 litres a day to prevent renal calculi and urate deposit.

• Report any changes in the respiratory status

• Avoid crowds and other probable sources of infection.

15. *Fluorouracil*

• Hold back the drug if WBC <3500/mm$^3$ or platelet count is < 100,000/mm$^3$

• Perform renal studies and hepatic studies.

• Check for inflammation of mucosa, dryness, soreness, white spots, ulceration of mouth.
• Watch for GI symptoms, including cramps, vomiting, nausea, stomatitis and increased frequency of stools.
• Diet should be highly nutritious with iron, dairy products, and vitamin supplements. Diet should be low fibre.

**Patient education**

• If stomatitis is present avoid intake of food with citric acid and rough texture.
• Avoid: use of aspirin, NSAID's, hard bristle brushes, sunlight to prevent photosensitivity. Do not receive vaccinations during the treatment.
• Teach and advice the patient to report signs of jaundice, anemia, infection and bleeding.
• Patient should avoid crowds, number of visitors should be limited, the patient should be advised to wear a mask while in public to avoid respiratory infections

16. Mercaptopurine

• Drug should be discontinued if WBC count is<3500 and platelet count is <100,000.
• Complete renal parameters (BUN, serum uric acid, electrolyte, urine creatine clearance rate) should be evaluated during the therapy.
• Report any incidence of oliguria, hematuria, bruising, fatigue, oral pain, mouth ulceration, bleeding, dysphagia, rash, itching, flushing, and urticaria.
• Administer antacid before giving the tablet. Drug should be given after evening meal before bed time.
• Diet should be rich in iron and low in purines. Vitamin supplements should be provided as prescribed.
• Oral hygiene should be given high importance, brush should be soft.
• Protective isolation and medical asepsis should be strictly followed if WBC count is low.

**Teach the patient**

• To report any oral ulceration, bleeding, white spots etc., food which contains citric acid, which has hot or rough texture, should be avoided.
• Increase fluid intake to 3 litres per day. Examine oral cavity regularly.
• Communicate to the patient signs of infection, haemorrhage, anemia, stomatitis blood dyscariasis etc.
• The care giver should intimate the prescriber the occurrence of any of the following: fever, breathlessness, sore throat, chills, vomiting, anorexia, nausea, diarrhoea, bleeding bruising etc.
• To take entire dose at one time.

17. Pemetrexed
• The drug should not be started if absolute neutrophil count is <1500cells/mm$^3$ platelet count is <100,000cells/mm$^3$ or urine creatinine clearance is less than 45ml/min.
• Rectal temperature is contraindicated.
• Rash flushing, itching and urticaria indicate severe anaphylaxis.
• The oral cavity should be regularly checked for dryness, bleeding, white spots, soreness, oral pain and dysphagia.
• Five daily doses of folic acid (low dose) must be taken 7 days prior to the treatment to act as a prophylactic measure to treat GI toxicity (hematologic).
• Use only 0.9%NaCl for reconstitution, follow aseptic techniques while reconstitution and administration. Unused portion after reconstitution must be discarded.

Patient education
• Report any incidence of side effect or any complaints to the nurse or prescriber.
• Contraceptive measures should be pursued during the treatment and up-to 8 weeks after the treatment completion. Breast feeding should be absolutely ceased.
• Avoid alcohol, live vaccines, salicylates commercial mouthwash and razors.

Anti-biotic agents
18. Bleomycin
• Before the administration of the first 2 doses of the medication IM test dose must be given in the lymphoma 1-2 units.
In product

Pulmonary function test and chest x-ray should be taken before the treatment and twice weekly during the treatment.

Anaphylaxis may occur, therefore the well-equipped emergency resuscitation trolley must be kept ready at all times.

Anti-emetics should be administered before giving the drug and continued up to 8 to 10 hours after treatment to prevent the vomiting.

The unused portion after reconstitution can be used up to 2 weeks if refrigerated and up to 24 hours at room temperature.

Place the patient in semi fowlers teach deep breathing exercise.

If patient is not nauseated or vomiting provide carbonated beverage.

Teach family and patient

To report side effects and complaints to the concerned health professional.

Avoid vaccination during the treatment, do not breast feed, use contraception,

Report any damage of oral mucosa.

19. Dactinomycin

With hold the drug if the WBC count is < 4000/mm$^3$ or platelet count falls below 75,000/mm$^3$

Perform complete renal studies before and during the therapy.

Monitor vital signs for any deviation from normal value, maintain intake output chart and report if the output falls below normal (30 ml/hr).

Hepatic studies should be performed every month or as needed after the commencement of the treatment.

Continuously assess the patient for signs and symptoms of complication (anemia, dehydration, anaphylaxis, jaundice, vomiting and diarrhoea).

Teach the patient

Use reliable contraception during the treatment and up to 6 months after treatment completion and do not breast feed.

Avoid crowds and other possible sources of infection.
- Inform any abnormalities (mouth ulcers, soreness of throat, signs of infection etc.) to the concerned health professional.

20. Daunorubicin

- Complete blood count, platelet count should be regularly assessed. If granulocyte (absolute) count is less than 750/mm$^3$ discontinue the drug.
- Watch the patient for any signs and symptoms of jaundice (yellowish discoloration of the skin and sclera, clay colored stools, dark urine, abdominal pain)
- Echo-cardiography, chest x-ray, and radio nuclide angiography should be taken. Congestive heart failure (CHF) characterised by weight gain, edema, crackles and jugular vein distention may occur after 2-6 months of treatment.
- In order to prevent nausea and vomiting administer anti-emetic ½ an hour before and up-to 10 hours after the drug administration.
- Advice the patient to avoid pregnancy during and up to 4 months after treatment.
- Advice to inform any break in the skin or mucosa, bleeding, diarrhea, hematuria etc.
- Warn the patient that urine and other body fluids may be in orange colour for up to 48 hours after drug administration.

1.14.19 In Vitro Screening Methods of Anticancer Agents

1.14.19.1. Ideal characteristics of an In vitro Screening method

An ideal screening in vitro method should be simple, economical, reproducible, rapid and sensitive. The assay should be applicable to large number of tumors types and test compounds. The choice of the cell lines should be representative of clinical situation as much as possible. The range of drug concentration used in vitro should be comparable to that expected for in vivo treatment. The global of screening assay is to test the ability of a compound to kill cells, at the same time, the assay should be able to discriminate between replicating cells and non-replicating cells. Different assays take advantage of various properties of cell as given below in Table 19
Table 19. Different Assays Shows Various Properties of Cell

<table>
<thead>
<tr>
<th>SI.No</th>
<th>Cell properties</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Enzymatic properties</td>
<td>Tetrazolium salt assay (MTT)</td>
</tr>
<tr>
<td>2</td>
<td>Protein content/synthesis</td>
<td>Sulphorhodamine B assay</td>
</tr>
<tr>
<td>3</td>
<td>DNA content/synthesis</td>
<td>$^3$H-Thymidine uptake \ Newer fluorescent analogues with flow cytometry</td>
</tr>
<tr>
<td>4</td>
<td>Membrane integrity</td>
<td>Dye exclusion tests</td>
</tr>
<tr>
<td>5</td>
<td>Clonogeneic properties</td>
<td>Clonogenic assay</td>
</tr>
<tr>
<td>6</td>
<td>Cell division</td>
<td>Cell counting assay</td>
</tr>
</tbody>
</table>

1.14.19.2 Tetrazolium salt Assay (Micro-culture Tetrazolium Test or MTT assay)

For anticancer drug screening MTT assay is internationally accepted. The assay is dependent on the cellular reduction of 3-(4, 5 dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide tetrazolium salt to a blue formazan product by the mitochondrial dehydrogenase of viable cells or metabolically active cells. The intensity of blue colored formazan produced is directly proportional to the cell viability. The cells from a particular cell line when in log phase of growth are trypsinized, counted in hemocytometer and adjusted to appropriate density in a suitable medium and the in different multi-well plates i.e. 96 well-plates. The cells are treated with various concentration of drugs for specific duration after which MTT dye should be added in each well and plates should be incubated at 37° C for 4h in a CO$_2$ incubator. The plates are then taken out of the incubator and dark blue colored formazin crystals are thoroughly dissolved in isopropanol / DMSO at room temperature. The plates are then read. Percentage of cell viability = OD of treated cell / OD of control cells x 100

The advantage of MTT assay is that it can be run on various concentrations and can be used to get an idea of the dose response relationship for each drug.
1.14.19.3 Sulphorhodamine B Assay (SRB)

SRB assay is used to measure the whole-culture protein content, which is supposed to be proportional to the cell number. Cell cultures are stained using a protein staining dye Sulphorhodamine. Sulphorhodamine B Assay is a bright pink anionic dye that binds with the basic amino acids of cells. Un-bounded dye is then washed with acetic acid, and protein-bounded dye is extracted using un-buffered solution. Tris base for determination of optical density in a computer-interfaced, 96 well microtiter plate reader. Since dead cell are either lysed or lost during the procedure, the amount of SRB binding is proportional to the number of live cells left in a culture after drug exposure. This assay can measure the cellular protein content of both adherent and suspension cultures. Screening capacity, reproducibility and quality control all appear to be enhanced in this assay relative to the tetrazolium salt assay.

1.14.19.4 $^3$H-thymidine Uptake Assay

In this assay tumor cell suspensions are bared to the drug continuously, for five days, after which a radio-labeled precursor i.e. $^3$H-thymidine is added during the final 48 hr of the assay to label proliferating cells. $^3$H-thymidine is incorporated into the DNA of the replicating cells, which can then be determined either by autoradiography or this assay can be performed by using liquid-scintillation counting.

This assay can be used for both adherent and suspension cell-lines. The assay suffers from the drawback of using radioactivity and being labor intensive. This assay is rapid relatively inexpensive and feasible for the common tumor types. Conversely it will not differentiate between malignant and non-malignant cell and might lead to false-negative predictions if fatally damaged cells undergoes a concluding division.

1.14.19.5 Fluorescence

Fluorescent dyes are normally used in conjunction with microscopic evaluation methods (assay in-vitro chemo-sensitivity assay). After drug-exposure; the cells are exposed to fluorescent-labeled precursors. The replicating cells will incorporate labelled precursor into their DNA and the resulting fluorescence is then measured by flow-cytometry. This assay requires the data to be analyzed by an expensive and sophisticated fluorescence activated cell-sorter FACS instrument. Because of technical difficulties in applying flow cytometry to
Introduction

“primary tumor specimens” data on the “predictive value” for clinical response for this assay are too scarce to permit definitive conclusions.

1.14.19.6 Dye Exclusion Tests

This method was mainly used because of its technical simplicity and ease in handling a number of specimens. These assays rely on the structural integrity of the cell. Dead cells would have lost membrane integrity and hence would take up vital dyes like tryphan blue. In this assay cell are incubated with drugs for 4 days. Dead cells are stained in suspension with fast green dye with or without nigrosin. The specimen is centrifuged and disks of cells are collected in the microscopic slides. The end point of the study is the morphologic identification of tumor cell cytotoxicity compared with the internal control standard of rythrocytes. The DiSc (Differential staining cytotoxicity) assay measures cell kill in both dividing and non-dividing tumor cell population.

1.14.19.7 Clonogenic Assay

A concern while using anti-proliferative assays is that, it measures growth inhibition rather than cell killing. Clonogenic survival assays measures loss of tumor cell reproductive viability i.e; the ability of a single cell to form colonies. It is the most direct method used for measuring cytotoxic activity of a drug. In this assay, tumor biopsies are used to prepare single cell suspensions and later they are exposed to anticancer agents. Cell are then rinsed and plated in a semisolid medium i.e. agar or methyl cellulose, a medium that precludes proliferation of non-malignant cells in the specimen. After 14 to 28 days some cells would have undergone several divisions and would have formed tumor colonies which can be quantified in a semi-automated or visual fashion. Non-replicating cells and dead cells are not counted in this case. The number of colonies from the treated cells is compared with the number of colonies from the untreated control cells and the fraction of control growth provides an index of drug activity. This assay is labor-intensive costly, and cannot be used for suspension cell lines.

1.14.19.8 Cell Counting Assay

Cells are cultured in the presence of drug for 2-5 culture-doubling times, after which the cell number is estimated using a hemo-cytometer or cell counter. The assay is easy to perform, rapid and can be used for both adherent and suspension cell lines. in cell counting
assay by the cell counter. The IC\textsubscript{50} of drugs (concentration of drug required to inhibit 50% cell growth) values can be calculated using above assay (Gupta (2009)).

1.14.20 Drug Combination Regimens Used in Cancer

The combined use of two or more drugs is often superior to a single drug therapy in most of the cancer. The following statements have been used in designing like treatment:

- Each drug used in the combination therapy of cancer should have individual therapeutic activity against the tumour being treated.
- More than two cycles of chemotherapy are hardly sufficient to eradicate a tumour. Hence, several (6 to 8) cycles of treatment should be given.
- The combined regimens should include drugs that act by different mechanisms. Like a combination provides additive (or) synergistic therapeutic effects.
- For the combination, drugs having different dose limiting toxicities should be selected so as to avoid cumulative damage to a single organ.

The following drug combination regimens have provided encouraging results in some selected malignancies (Sharma 2008).

- **Acute lymphocytic leukaemia (ALL)**
  For induction: vincristine (oncovin) + prednisolone + asparaginase ± doxorubicin (or) vincristine + prednisolone
  For maintenance: mercaptopurine + methotrexate ± cyclophosphamide

- **Acute Myeloid Leukaemia (AML)**
  For Induction: Cytarabine + daunorubicin (or) mitoxantrone (or) idarubicin)
  For maintenance: same as above or etoposide

- **Chronic lymphocytic leukaemia (CLL)**
  Fludarabine + prednisone (or) fludarabine + cyclophosphamide + mitoxantrone + dexamethasone (or) chlorambucil + prednisone (or) alemtuzumab

- **Chronic myeloid leukaemia (CML)**
  Imatinib; Hydroxyurea; Interferon alfa.

- **Hairy cell leukaemia (HCL)**

Department of Pharmacy, JJT University, Rajasthan
Pentostatin (or) Cladribine (or) Interferon alfa

- **Hodgkin’s disease**
  Doxorubicin (Adriamycin) + bleomycin + vinblastine + dacarbazine (ABVD regimen) (or) mechlorethamine + vincristine (oncovin) + procarbazine + prednisone (MOPP regimen).

- **Non–Hodgkin’s lymphoma**
  Cyclophosphamide + doxorubicin + vincristine (oncovin) + prednisone [CDOP (or) CHOP regimen; earlier doxorubicin was named as hydroxydoxorubicin] + retuximab (for better results).

- **Breast cancer**
  Stage 1: breast surgery followed by tamoxifen
  Stage 2: postoperatively, cyclophosphamide + methotrexate + 5-fluorouracil (CMF protocol)
  Stage 3 and Stage 4: Cyclophosphamide + Adriamycin (doxorubicin) + 5-flourouracil (CAF protocol) (or) Paclitaxel + trastuzumab (or) aromatase inhibitors like anastrozole, letrozole (or) exemestane with adjuvant chemotherapy, for hormone receptor positive cancers.

- **Cancer lung**
  Small cell (oat cell): cisplatin + etoposide
  Non small cell: cisplatin + gemcitabine (or) vinorelbine (or) paclitaxel (or) gefitinib

- **Melanoma**
  Dacarbazine (or) interferon alfa (or) cisplatin

- **Kaposi’s sarcoma**
  (A multifocal malignant neoplasm of reticuloendothelial cells involving skin-often associated with AIDS): doxorubicin (Adriamycin) + Bleomycin + vincristine (ABV protocol)

- **Insulinoma**
  Streptozocin (or) interferon alfa

- **Osteogenic sarcoma**
Introduction

Methotrexate + leucovorin (or) doxorubicin (but after surgery)

- **Ewing’s sarcoma**
  Cyclophosphamide (or infosfamide) + doxorubicin (Adriamycin) + vincristine (CAV protocol)

- **Carcinoma of Cervix**
  Cisplatin + methotrexate + doxorubicin + vinblastine

- **Stomach cancer**
  Cisplatin + Fluorouracil + leucovorin + Fluorouracil (ELF protocol)

- **Carcinoma of Ovary**
  Cisplatin + methotrexate + doxorubicin + vinblastine

- **Endometrium Carcinoma**
  Progestins (or) Tamoxifen

- **Cancer pancreas**
  Gemcitabine (or) docetaxel (or) ELF protocol

- **Cancer Rectum/Colon**
  Fluorouracil + leucovorin + Irinotecan

Cancer chemotherapy, as currently employed, can be curative i.e; 40-80 % success rate in certain disseminated neoplasms. These include: **In adults**: Hodgkin’s disease, Non-Hodgkin’s disease, Testicular carcinoma and Choriocarcinoma. **In children**: Acute lymphocytic leukaemia (ALL). Ewing’s sarcoma, Retinoblastoma, Wilm’s tumour (malignant tumour of skeletal muscle).
1. 15 Plant Profile

_Urena lobata_ Linn.

**Botanical Name**: _Urena lobata_ Linn.

**Common Name**: Caesar weed

**Parts Used**: Leaves, Stem, Root and Whole plant

![Urena lobata Linn](image)

Fig 7. _Urena lobata_ Linn

1.15.1 Taxonomical Classification

- **Kingdom**: Plantae
- **Unranked**: Angiosperms
- **Unranked**: Rosids
- **Order**: Malvales
- **Family**: Malvaceae
- **Subfamily**: Malvoideae
- **Tribe**: Hibisceae
- **Genus**: Urena
- **Species**: _U. lobata_

**Synonyms**: _U. Americana, U. grandiflora, U. trilobata Vell., Urena diversifolia_

_Department of Pharmacy, JJT University, Rajasthan_
1.15.2 Vernacular names

Vernacular names of the plant are shown in Table 20.

Table 20. Vernacular Names of *Urena lobata*

<table>
<thead>
<tr>
<th>SI. No.</th>
<th>Languages</th>
<th>Vernacular Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hindi</td>
<td>Bachata, Bachit, Bachita, Bala Bhed, Brachta, Chatkura, Dudh-Khal, Kapasi, Kunjia, Lapetua, Lotloti, Unga, Vilaiti San</td>
</tr>
<tr>
<td>2.</td>
<td>Malayalam</td>
<td>Urppam, Udiram, Uram, Uran, Uren, Vatti, Vatto</td>
</tr>
<tr>
<td>3.</td>
<td>Kanada</td>
<td>Baralu Kaddi Mara, Bakkina Hejje Gida, Dodda Bende, Dooda Bende, Hamsapaadi, Kaadu Thutthi, Otte, Otte Mara, Vatta</td>
</tr>
<tr>
<td>4.</td>
<td>Marathi</td>
<td>Rantupkada, Rantupkuda, Tupkato, Vanabendha, Vana-Bhenda, Vanbhendi, Wagdau Bhendi</td>
</tr>
<tr>
<td>5.</td>
<td>Sanskrit</td>
<td>Vanabhenda, Nagabala, Bala, Atibala</td>
</tr>
<tr>
<td>6.</td>
<td>Tamil</td>
<td>Ottatti, Ottattutti, Ottu, Thuththi, Ottukututti, Ottuttutti, Ottuttutti</td>
</tr>
<tr>
<td>7.</td>
<td>Telegu</td>
<td>Nalla Benda, Nallabenda, Padanikaada, Pedda Benda, Peddabena, Peddabenda, Piliyamankena, Vana Benda</td>
</tr>
<tr>
<td>8.</td>
<td>English</td>
<td>Aramina Fibre, Congo Jute, Cousin Mahoe, Guaxima</td>
</tr>
</tbody>
</table>

1.15.3 General Description of *Urena lobata* Linn

Caesar weed called as, Bur Mallow, Aramina, Hibiscus Bur and Pink Chinese Burr. It is a sub shrub of 60 cm to 300 cm in altitude and basal diameter is 7 cm. Bark is downy and is hard and fibrous, within the bark is green in color and outside it is brown in color. The wood is medium in density and pale yellow in color. The herb is sustain through lateral and tap root arrangement. The color of root is ivory or brown. The root system is
flexible and hard-hitting roots. The plant is typically having a solitary stem rising from the land. However the plant generates more than a few stems and main twigs are having small shoot and a lot of twigs are present in the whole life time of the plant.

Dis-colorous, grayish-green, alternating leaves are pubertal on below and above the leaf. Leaves are angulated, oval in shape and lobbed as shallow of 1 to 12 cm. They have margins of indent shape. The shape of the fruit is globose and of 8 mm to 10 mm of capsules shape and it is having mericarps of five smooth barbed. The plant grows throughout moist tropic and subtropical regions (Liogier 1994).

**Habitat:** *Urena lobata* Linn, is a herbaceous, upright and semi-woody in nature. It is coming under shrub growing, tomentose and 60 - 100 cm or more height. The young stem as well as branches are covered with somewhat harsh spreading stellate hairs (tomentum) and bearing simple, alternate variable broadly ovate to round cordate, angled or lobed leaves and sessile or shortly stalked pinkish auxiliary flowers.

**Leaves:** Leaves of the plant are simple, alternate, petiolate and stipulate, blade-very variable. Usually the leaf is broader than long round or ovate, up to 10-15 cm long, cordate at the base angled or shallowly 5-7 lobed, the lobes not extending half way down, nearly obsolete and acute or acuminate, serrate, stellately tomentose on both surface. But, paler beneath with five to seven pairs of basal nerves which are prominent on the surface (down) and below the basement region there is a large gland and occasionally at the base of two lateral also.

**Flowers:** Pink colored flowers of axillary shape, petals are of five in number. The size of about 1 cm in board. Flower of the herb is shown in Fig 7.

---

*Fig 8. Flower of Urena lobata*
Petiole: Variable in length.

Stem: Moderately thick, pubescent in young ones and smooth in mature ones, with long internodes.

Root: The root system consists of the taproot and several branching lateral roots are fairly stout and brown in colour. These may attain a diameter of 5-6 mm and length varying from 20-25 cm. Very small wiry cream color rootlets arise from the lateral roots. Small lenticels are also present towards to base and the outer surface of the root.

1.15.4 Major chemical constituents

The main constituents of *Urena lobata* Linn include flavonoids and glycosides such as β-sitosterol, stigmasterol, furocoumarin, imperatorin, mangiferin and quercetin (Keshab 2004). It also contains kaempferol, luteolin, hypolatin and gossypetin.

1.15.5 Geographical source

Caesar Weed belongs to Asia. Herb breeds all through damp sub-tropic and tropical province counting India, Florida, Hawaii, Guam, Louisiana and in American Samoa.

1.15.6 Environmentalism

*Urena lobata* freely grown in anxious region, particularly badly cope scarified-pastures and eroded-areas, and it is a plantation of perennial category. This herb is having difficulty to yield yearly crop. Herb does not grow in wood-canopies. This plant is not struggle healthy in giant meadow and brush-lands.

1.15.7 Cultivation

Seed propagation is the method of cultivation of *Urena lobata*. Before sowing the seeds, it has to soak in water for 90 min. It will result a high germination rate of 96%. The seeds are discrete by adhere to fur and clothing. The small seedlings are planted on the well-prepared land.

Soil

The plant will grow in a different range of soil. Fertility range also differs and the new plant will get fertilizer from parent-materials. It will not cultivate in saturated oil where all the minerals exhausted. It is having the capacity to withhold the salt in the soil. Water it is need for its healthy cultivation of the herb.
1.15.8 Growth and management

*Urena lobata* grow very fast and it will reach height of 0.5 to 2 m in tall in the first year itself. After the first season it will dry i.e. its second year of its first of growth we can collect the fiber after 7-8 months from the plant. It will yield a fiber of 1800 kg/hectare. These fibers are recognized from seeds only. 300-500 kg/ha seeds are getting from the plants of 7 -8 months of age.

1.15.9 Benefits and Detriments

This herb grows as colonies in the concerned area. This growing nature of the plant help to guard the soil, whereas provides wrap in support of natural world. The gorgeous flowers which will contribute to the aesthetic area which hare colonized. Aramina is the fiber which will obtain from this herb, which looks like jute fiber. Congo-jute is the fiber manufactured in Africa and Brazil from the same plant (*Fagundes 2003*). A variety of extract obtained from the roots and leaves from the plant are benefits as herbal-medicine. These extracts are used for varieties of disease like malaria, wounds, toothache, fever, colic and joint-pain.

A report shows the raw leaves of *Urena lobata* hold the phosphorous of 67 mg/100g, ash of 21gm, 0.1 gm of fat, 3.2 g protein, 12.8 gm of carbohydrates, moisture of 81.8 %, Calcium of 558 mg and fiber of 1.8 gm. Leaves of Caesar weed give a semi-purified glycoside which is 86 % as effectual as the aspirin which is used as anti-inflammatory medicine in rats. In Africa the flowers and leaves are used as a famine food. The animal fur and the burs that are collected on clothing are a nuisance. On the other hand, the plant can become a harsh-weed in plantations and pastures and it is slight browsed by the cattle.

1.15.10 Uses

The traditional uses of the plant were found to be diuretic, febrifuge and rheumatism. It severs as food for animals as well as humans (*Mazunder et al 2001*). It is used for malaria, gonorrhea, wounds and toothache.
1.16 Review of Literature

Gupta et al (2004), investigated the antioxidant property of the leaf extract using methanol as solvent. The herb selected for this study was *Ervatamia coronaria* which belongs to the family of Apocynaceae. NO (nitric oxide radical), hydroxyl radical, superoxide anion radical (SOD) and DPPH radical assays were used to investigate the antioxidant property of the herb. Due to the several phenolic hydroxyl groups in tannins, flavonoids and polyphenols, they became precious plant active constituents in the hunting action. As a result, the reductive capability, radical scavenging activity, and anti-lipoper oxidant activity strongly suggests that the plant had anti-oxidant and anti-lipoper oxidant activities. The outcome obtained in this present work indicated that methanol extract of *Ervatamia coronaria* leaves was a possible source of natural antioxidant.

Morelli et al (2006), conducted a study, in which two triglycerides namely α-palmitoyl-β-linoleoyl-α'-linoleoyl glycerol and α-linoleoyl -β-linoleoyl-α'-oleoyl glycerol were secluded from the hexane extract of *Urena lobata*. Both bearing polyunsaturated fatty acid residues. These two compounds were characterized by the presence of three different poly-unsaturated fatty acids and their structures were studied and illustrated by various spectral methods.

Lissy et al (2006), indicated that *Sida retusa*, *Urena lobata* and *Triumfetta rhomboidea* possessed significant antioxidant activity, and the quantity of *Sida retusa* root extract required for 50% inhibition of lipid peroxidation, scavenging hydroxyl radical and superoxide radical was 1130.24 µg/ml respectively. The investigation concluded that *Sida retusa*, *Urena lobata* and *Triumfetta rhomboidea* possessed significant antioxidant activity.

Daniels et al (2006), investigated the medicinal value of Native American medicinal flora which is traditionally used for the treatment and prevention of a variety of diseases. These herbal preparations are suspected to have various biological characteristics useful for the suppression or simulation of immunological response. They are also alleged to have anti-proliferative effect on neoplastic cell. In this study two Native American plants (*Ligusticum porteri* (Osha) *Anemopsis californica* (Yerba Manza)) were selected. Aqueous and ethanol extracts from these two plants were obtained and its effects were investigated on the growth of human HCT8/E11 colon and MCF-7/AZ breast cancer cells. The result obtained was as follows: aqueous and ethanol extracts obtained from *Anemopsis californica* repressed the
Introduction

growth of breast cancer cell (MCF-7/AZ) in a concentration dependent manner. However it had no influence on HCT8/E11. Extracts taken from L. porteri was inactive on both cell lines. It was further observed that when exposed to both (aqueous and ethanolic) extracts from A. californica, activities of signal regulated protein ERK1/2 (kinase 1 and 2) were markedly decreased. Therefore the conclusion was that, the growth inhibitory effect of A. californica in breast cancer cell is kinase 1 and 2 mediated.

Chatterjee et al (2007), detected DNA A and satellite DNA β molecule from Urena lobata. This study was conducted for the first time in the Eastern division of India. This work showed yellow vein mosaic disease symptoms in the plant. Nucleic acid spot hybridisation (NASH) examination was performed by means of α-32P radio labeled prod corresponding to the clone of a complete DNA β molecule and DNA A coat protein gene tests. The first proof of begomo-virus was confirmed by using PCR amplification technique with both DNA A and satellite DNA β molecule. DNA β and DNA A molecule are connected with the yellow vein mosaic disease of the herb Urena lobata.

Adeloye et al (2007), deliberated the antioxidant, antimicrobial and the phytochemical investigation of U. lobata leaf extract. Compounds of ethyl acetate fractions are separated. These compounds structures were resolute based on spectroscopic data. The compounds which are separated from the ethyl fractions showed anti-microbial activity against different organisms like Escherichia coli, Bacillus subtilis, Klebsiella pneumoniae, Bacillus polyxyma and Candida albicans. This work was fulfilled that, the isolated flavanoids compounds are responsible for the biological activity of Urena lobata. Therefore, this work supports the conventional uses of this plant in the management of infections.

Kumarappan et al (2007), determined the in-vivo antitumor activity of the polyphenolic extract of the leaves of the plant Ichnocarpus frutescens on Ehrlich ascites carcinoma cell lines. In-vitro antitumor activity was determined by using two types of cell line called as K-562 (erythro-leukemia) and U-937 (monocytoid leukemia). Antioxidant property was investigated for the polyphenolic extract, of the leaves of the plant Ichnocarpus frutescens as opposed to nitric oxide I and superoxide radicals. This study has accomplished that polyphenolic extract of Ichnocarpus frutescens possess good antitumor property by in-vitro and in-vivo antioxidant activity.
Fatma et al (2007). Obtained 76 ethanolic extracts of medicinal herbs, (belonging to 67 species and 34 families) from the Jordanian flora. These were studied for their antiproliferative activity on a breast carcinoma cell-line (MCF-7). Cell culturing was done in a medium of RPMI 1640 and was incubated with the extracts for 3 days. Cytotoxicity was evaluated using the Sulphorhodamine B (SRB) assay. From the tested crude extracts, potent antiproliferative activity was seen in Conyza canadiensis, Inula graveolens, Achillea santolina and Saliva dominica, and the activity resided in the extracts obtained from chloroform/ethanol. The most active plant was I. Graveolens (with an IC$_{50}$ of 3.83µg/ml). In all active extracts, phytochemical screening indicated the occurrence of phenolics, flavonoids, and terpenoids. These results suggested the possible use of medicinal plants from Jordanian flora as anti-neoplastic agents in the near future.

Nooman et al (2008)., studied the methanol extracts of regularly used medicinal plants and were investigated for their antioxidant property. Ascorbic acid was used as the standard antioxidant drug for this study. Green tea, Camellia sinensis L and other plants such as black tea showed the greatest antioxidant activity, Eugenisa caryophyllus are showed in descending order of the antioxidant properties. Trigonella foenumgraecum, Piper cubea L, Zingiber officinale Roscoe and Piper nigrum L and Elettaria cardamomum are showed very fragile free radical scavenging activity by the DPPH method.

Lee et al (2008)., determined the capability of mycelial extract of Clavicorona pyxidata (DGUM 29005) inhibiting the activities of Acetylcholinesterase (AChE) and beta-secretase (BACE). Rat (pheochomocytoma PC12) cells in the culture were not determined to be vulnerable to the cytotoxic activity as verified by the mycelial extract. The ethanolic extract repressed the endogenous AChE activity in PC12 cellular homogenates. IC$_{50}$ value was found to be 67.5micro/ml. These results suggests that the Clavicorona pyxidata mycelial extract has the potential to augment cholinergic functions and therefore, it may results in a function in the amelioration (improvement) of the cholinergic deficit observed in cases of Alzheimer’s disease as well as other types of age-associated memory impairment.

Odimegwu et al (2008)., investigated a herbal ointment containing Dissotis theifolia extract, for wound healing and antibacterial activities against clinical wound isolates of Staphylococcus aureus and Pseudomonas aeruginosa. Results of uninfected wounds indicate
that, in corporation of *Dissotis theifolia* extract 60, 90 and 120 mg/g in to the applied ointment enhanced the rate of wound closure. *Dissotis theifolia* extract reduced the epithelialization period and for the control group compared with blank ointment to 8.8 ± 0.2 days for the group treated with 120 mg/g of *Dissotis theifolia* ointment. Similarly, the rate of wound healing of excision wounds infected with clinical isolates of *Staphylococcus aureus* were higher for the groups treated with *Dissotis theifolia* ointment.

Chitra et al (2009), studied the wound-healing property of dissimilar extracts of *Allium cepa* Linn of Liliaceae family. Alcoholic extract of the plant *Allium cepa* showed better wound-healing activity in the entire models, as compared to chloroform and chloroform water extracts. This property may be due to the free radical scavenging action of the herb. From these investigations, the studies concluded that alcoholic extract of tubers of *Allium cepa* has significant wound healing activity.

Sanjay et al (2009), conducted a study to evaluate the antineoplastic effect of the solanum nigrum fruit on HeLa(Helen lane) cell line and Vero cell line. Methanolic extract of the given fruit were tested for its inhibitory effect on HeLa cell line. Trypan blue dye exclusion method was used to determine the percentage viability of the cell line. Sulphorodamine B (SRB) assay and micro culture tetrazolium (MTT) assay was used to evaluate the cytotoxicity of solanum nigrum on HeLa cells. When used in a concentration range between 10mg/ml to 0.0196mg/ml by using SRB assay, solanum Nigrum Methanolic extract showed significant cytotoxicity effect on HeLa cells. Inhibitory action was also exhibited on HeLa cell line in the same concentration range by using MTT assay. From the performed assay Methanolic extract of the drug showed greater activity on Helen Lane cell line when compared to Vero cell line, therefore effectively establishing that solanum Nigrum can be used for its anti-cancer activity.

Shaida et al (2009), Carissa carandas extracts were screened for their anticancer activity. A three step extraction protocol using n-hexane, chloroform and methanol as the solvent systems was carried out on the leaves, the unripe and ripe fruits of *Carissa carandas*. In the present study, plant extracts were tested for their effectiveness as anticancer agent on the human ovarian carcinoma, Caov-3 and the lung cancer cells, NCI. Chloroform extract from leaves showed good anticancer activity against the Caov-3 with the EC50 value of 7.702µg/ml while the n-hexane extract of the unripe fruit exhibits a remarkable activity.
towards the NCI with the EC50 value of 2.942µg/ml when assayed using the methylene blue assay (MBA).

**Dogra (2009),** studied the bio activities of four trifoliate plants (glycine max (control), Cajanus cajans, Phaseolus vulgaris and Tecoma stans) found in Nagpur region. Using chloroform, petroleum ether, methanol and water as solvents, plant extracts were prepared by Soxhellation. Anti-bacterial activity was evaluated using agar well diffusion method against seven bacterial strains including Escherichia coli (MTCC 1652), Pseudomonas aeruginosa (MTCC 441), staphylococcus aureus (MTCC 740), Proteus mirabilis (MTCC 425), bacillus subtilis (MTCC 441), Proteus vulgaris (MTCC 426) and salmonella typhi (clinical sample). Anti-cancer activity was assessed against MCF7 and HeLa cancer cell lines initially by means of visual examination and later followed with MTT based cytotoxicity assay and Cell Viability Count. Chloroform extracts showed anti-bacterial activity against both gram-positive and gram-negative bacteria. Extract of Cajanus cajans were most effective and pseudomonas aeruginosa was the most susceptible to the extracts. The best anti neoplastic activity was demonstrated by methanol extracts of all the selected plants. However the extracts did not show any activity against HeLa cells. It was thus concluded that extracts from the above mentioned plants can be used for their antibacterial and anti-cancer properties.

**Istvan et al (2009),** conducted a study with the aim to scrutinize the anti-cancer characteristics of five alkaloids isolated from Amaryllidaceae. They also intended to study the apoptosis inducing capacity and the inhibitory effect on P-glycoprotein. With the help of rhodamine-123 (Rh-123) assays, the tested alkaloids were evaluated for their MDR (multi drug resistance)-reversing activity on human MDRI-gene transfected L5178 mouse lymphoma cells. In comparison to the untreated cell, intracellular Rh-123 concentration was increased by 30 and 50 fold using trisphaeridine and pretazettine respectively. Trisphaeridine and 2-O acetylllycorine were validated by means of checkerboard method to enrich the anti-proliferative property of doxorubicin on L5178 multi drug resistant mouse lymphoma cells. MTT(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay revealed that, trisphaeridine, 2-O- acetylllycorine and pretazettine displayed excellent anti-proliferative effect on both mouse and human cell lines.
**Introduction**

Yaman et al (2010), investigated to compare the effects of *Nigellea sativa* and silver sulfadiazine (SSD) cream on healing of burn-wounds in the rats. In a burn-wound model it was to be found to shorten the healing process both histo-pathologically and statistically as compared to SSD and the control group. Though it is antimicrobial, antioxidant, anti-inflammatory and immune-modulatory effects, *Nigella sativa* can be used as an adjunctive or alternative agent to existing wound healing therapies in future.

Kathriya et al (2010), studied the antioxidant and antitumor activities of the ethanolic extract of the plant *Oxalis corniculata* Linn. EAC cells were selected for both activities which were induced in Swiss Albino mice. Cyclophosphamide of 25 mg/kg b.w was used as a standard drug for the antitumor activity. In this study biochemical factors like albumin, total protein, alanine aminotransferase, lipid peroxidation, aminotransferase, enzymatic oxidation and alkaline phosphatase were examine. The study can be accomplished that ethanol extract of *Oxalis corniculata* Linn was slow down tumor enlargement in solid and ascetic cancer models. Antioxidant investigations and bio-chemical parameters were prop-up (support) the antitumor properties of the same.

Sermakkani et al (2010), investigated in-vitro activity of the methanolic extract of *Cassia italica* as oppose to vero and Hepo-2 cell lines. This plant belongs to Caesalpiniaceae family. This study shows the cytotoxicity activity was found to more in 1.25 mg/ml of the extract of methanol. This investigation has been concluded that, this herb can be used for cytotoxic agent.

Kanal et al (2010), investigated the pharmacognosy of stem bark of *Careya arborea* Roxb of Lecythidaceae family. Phytochemical investigations disclosed the presence of glycosides, phenolic compounds, carbohydrates and tannins in ethanolic and the aqueous extracts. High Performance Thin Layer Chromatography (HPTLC) outlines the standardization and authentification of the herb. Gums, amino acids, benzene, flavonoids and proteins were absolutely absent in the entire extracts. Lenticular openings at several part of the bark, starch grains are present in the medullary rays; crystals of prismatic type are there in secondary phloem and fibroid sclereids are helpful for the identification of the crude drug.

Shanthy et al (2011), carried out a study on Indian-medicinal herbs which are traditionally used for cancer. *In-vitro* cytotoxicity has been studied using Sulforhodamine (SRB) assay.
The extracts (ethanol and water) were tested against HT-29 and HT-15 (colon cell line), IMR-32 (neruoblastoma cell line) and A-549 (lung cancer cell lines). The study has been concluded that, the herbs such as Cannabis sativa, Colotropis procera and Ocimum sanctum possess a excellent cytotoxicity action.

Sini et al (2011), studied the antioxidant activity and radical scavenging action of the methanolic extracts of different plants. These plants are used by Tribes of Kerala for the traditional plant in different ailments. Antioxidant activity of these plant extracts were evaluated against DPPH free radical. In this work, Trianthema decandra showed the highest antioxidant activity. Capparis zeylanica, Plumbago zeylanica, Anisomeles malabarica Cassia occidental, Clitoria ternatea, and Trianthema decandra, revealed that they are having well-built antioxidant activity when compared to the other plants in this study.

Mehmet et al (2011), reviewed on experimental tumors which have great importance in modeling. Ehrlich ascites carcinoma is one of the commonest tumors and originally it is a hyper diploid. The EAC cells resemble the human tumors and are the most responsive to the chemotherapy treatment since they are undifferentiated. The EAC cells have a rapid development speed. Anti-cancer agents obtained from nature such as dactinomycin and doxorubicin derived from microorganisms and vinblastine, irinotecan, topotecan, vincristine and taxanes from plants that are used often during the recent years.

Tulika et al (2011), conducted a study to examine the anti-cancer potential of the extract taken from the seeds of Ziziphus Mauritiana in-vitro vs various cancer cell line (HL-60, Molt-4 and HeLa) and normal cell line HGF (Human Gingival Fibroblast) by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay as well-as in-vivo against EAC (Ehrlich ascites carcinoma). Proliferation of HL-60 cells was found to be markedly inhibited by the extracts. In the treated HL-60 cells Annexin and PI binding indicated, induction of apoptosis by the extract in a dose dependent manner. At the concentration of 20µg/ml and above, a prominent increase in sub-G0 population was revealed in cell cycle analysis. Potent anticancer potential was exhibited by the extract in vivo. The extract effectively reduced the tumour volume and viable tumour cell count. Extract treated animals also showed enhanced antioxidant status.
Harsahay et al (2012), studied the free radical properties of 2 memory enhancer medicinal herbs i.e. Baccopa monnieri and Centella asiatica. The study was carried out by measuring the reducing ability of the free scavenging activity by hydrogen peroxide. DPPH method also used to evaluate the antioxidant property of the same. Standard drug used was ascorbic acid in this study. Baccopa monnieri is having the higher concentration of total phenols and tannins when compared to Centella asiatica. The study was concluded that regular use of Baccopa monnieri as a supplement could be more useful when compared to Centella asiatica. Baccopa monnieri can be used in treatment for the neurological disorders which are caused by the free radical injure.