CHAPTER –I

GENERAL INTRODUCTION
1.1. **ANTICANCER AGENTS**

Cancer is a cellular disease, characterized by progressive loss of the organized properties of differentiated cells like growth control, karyotypic stability, morphological and biochemical traits and the definite location of cells within the organism. The disease is yet to be conquered by the power of medicine. It is due to its uncontrolled proliferative tendency that cancer cells have the capacity to form invasive and metastatic tumors. Malignancy at the cellular level involves genetic alterations in the form of activation of oncogenes or loss of function of tumor suppressor genes due to gene amplification, rearrangement, deletions and mutations and inhibition of apoptosis by increased $bcl-2$ expression. Till date cancer management is achieved by extensive usage of radiotherapy, chemotherapy, surgery and hyperthermia all of which either remove or kill neoplastic cells. Cancer is known to occur at almost any site in the body ranging from localised skin cancer to whole body leukemia (blood cancer). Systemic chemotherapy is the major treatment modality for a number of common cancers such as lymphomas, leukemia, melanoma and majority of disseminated tumors. The initiation of the disease process may involve any one or more of the following,

- Carcinogenic chemicals present in cigarette smoke,
- Industrial pollutants and the diet,
- Radiation,
- Oncogenic viruses,
• Genetic predisposition, and
• The aging process.

The dreaded disease of cancer currently remains one of the major causes of death in the world, despite many advances that have been made in chemotherapy and other mode of treatment. An ideal anticancer agent has not yet been discovered because of the reasons like lack of selectivity, frequent development of drug resistance and severe toxicity.

The majority of chemotherapeutic anticancer drugs can be divided into alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other antitumor agents. All of these drugs affect cell division or DNA synthesis and function in some way. Some newer agents do not directly interfere with DNA. These include monoclonal antibodies and the new tyrosine kinase inhibitors e.g. imatinib mesylate (Gleevec or Glivec), which directly targets a molecular abnormality in certain types of cancer (chronic myelogenous leukemia, gastrointestinal stromal tumors). These are examples of targeted therapies. In addition, some drugs that modulate tumor cell behavior without directly attacking those cells may be used. Hormone treatments fall into this category.

1.1.1. **Alkylating agents**

Alkylating agents are so named because of their ability to alkylate many nucleophilic functional groups under conditions present in cells. Cisplatin, carboplatin and oxaliplatin are alkylating agents. They impair
cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl and phosphate groups in biologically important molecules. Other agents are mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide. They work by chemically modifying a cell's DNA.

1.1.2. **Antimetabolites**

Antimetabolites masquerade as purines (azathioprine, mercaptopurine) or pyrimidines which become the building blocks of DNA. They prevent these substances from becoming incorporated into DNA during the "S" phase (of the cell cycle), stopping normal development and division. They also affect RNA synthesis. Due to their efficiency, these drugs are the most widely used cytostatics.

1.1.3. **Plant alkaloids and terpenoids**

These alkaloids are derived from plants and block cell division by preventing microtubule function. Microtubules are vital for cell division and without them, cell division cannot occur. The main examples are vinca alkaloids and taxanes.

- **Vinca alkaloids**: Vinca alkaloids bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules (M phase of the cell cycle). They are derived from the Madagascar periwinkle, *Catharanthus roseus* (formerly known as vinca rosea). The vinca alkaloids include vincristine, vinblastine, vinorelbine, and vindesine.

- **Podophyllotoxin**: Podophyllotoxin is a plant derived compound which is said to help with digestion as well as used to produce two other
cytostatic drugs, etoposide and teniposide. They prevent the cell from entering the G1 phase (the start of DNA replication) and the replication of DNA (the S phase). The exact mechanism of its action is not yet known. The substance has been primarily obtained from the American Mayapple (*Podophyllum peltatum*). Recently it has been discovered that a rare Himalayan Mayapple (*Podophyllum hexandrum*) contains it in a much greater quantity, but, as the plant is endangered, its supply is limited. Studies have been conducted to isolate the genes involved in the substance's production, so that it could be obtained recombinantly.

- **Taxanes**: The prototype taxane is the natural product paclitaxel, originally known as taxol and first derived from the bark of the Pacific Yew tree. Docetaxel is a semi-synthetic analogue of paclitaxel. Taxanes enhance stability of microtubules, preventing the separation of chromosomes during anaphase.

### 1.1.4. Topoisomerase inhibitors

Topoisomerases are essential enzymes that maintain the topology of DNA. Inhibition of type I or type II topoisomerases interferes with both transcription and replication of DNA by upsetting proper DNA supercoiling. Some type I topoisomerase inhibitors include camptothecins irinotecan and topotecan.
1.2. **ANTIMICROBIAL AND ANTIINFLAMMATORY AGENTS**

Antimicrobials are agents (or drugs) that kill or slow the growth of bacteria. They may be natural or semi synthetic or synthetic drugs which inhibit or kill bacteria. This capability makes them unique for the control of deadly infectious diseases caused by a large variety of pathogenic bacteria. Specific antimicrobials are necessary for the treatment of specific pathogens. In common usage, an **antibiotic** (from the Ancient Greek: *anti-* against, and *bios-*life) is a substance or compound that kills bacteria or inhibits its growth. Treatments for many infections prior to twentieth century were based on medicinal folklore. Plants and molds with antimicrobial properties were described over 2,500 years ago by ancients. Scientific endeavors understand the science behind what caused these diseases, the development of synthetic antibiotic chemotherapy, and the isolation of natural antibiotics marked milestones in antibiotic development.

Originally the antibiosis was known as drugs that had actions against bacteria. The term antibiosis, which means "against life," was introduced by the French bacteriologist Vuillemin as a descriptive name of the phenomenon exhibited by these drugs. These drugs were later renamed antibiotics by Selman Waksman, an American microbiologist in 1942. Synthetic antibiotic chemotherapy as a science and the story of antibiotic development began in Germany with Paul Ehrlich, a German medicinal scientist in the late 1880’s. Dr. Ehrlich noted that certain dyes
would binds and color human, animal or bacterial cells, while others did not. He then extended the idea that it might be possible to make certain dyes or chemicals that would act as a magic bullet or selective drug that would bind to and kill bacteria while not harming the human host. After much experimentation, screening hundreds of dyes against various organisms, he discovered a medicinally useful drug, the man made antibiotic salvarsan. However, the adverse side effect profile of salvarsan, coupled with the later discovery of the antibiotic penicillin, superseded its use as an antibiotic. The work of Ehrlich, which marked the birth of the antibiotic revolution, was followed by the discovery of prontosil, the first commercially available antibacterial antibiotic was developed by a research team led by Gerhard Domagk in 1932 (Who received the 1939 Nobel Prize for Medicine for his efforts) at the Bayer laboratories in Germany. The discovery and development of this first sulfonamide drug opened the era of antibiotics. Following their 20th century triumph in human medicine, antimicrobials have also been used increasingly for the treatment of bacterial disease in animals, fish and plants. In addition, they became an important element of intense animal husbandry because of their observed growth enhancing effect, when added in sub therapeutic doses to animal feed. Antimicrobials are also used in industry, e.g. to eliminate bacterial growth on the inside of oil pipelines. It is estimated that about half of the total amount of antimicrobials produced globally is used in food animals.
1.2.1. **Antiinflammatory agents**

Inflammatory diseases including different types of rheumatic diseases are a major cause of morbidity of the working force throughout the world. Inflammation is a normal protective response to tissue injury caused by physical trauma, noxious chemicals or microbiological agents. Inflammation is a body response for tissue repair. Inflammation is triggered by the release of chemical mediators which vary with the types of inflammatory process and include amines such as histamine, serotonin and lipids such as prostaglandins and small peptides such as kinins. The acute inflammatory response has three main functions.

- A transient material called the acute inflammatory exudates occupies the affected area. The exudates carry proteins, fluid and cells from local blood vessels into the damaged area to mediate local proteins.
- If an infective causative agent (e.g. bacteria) is present in the damaged area it can be destroyed and eliminated by components of the exudates.
- The damaged tissue can be broken down and partially liquefied and the debris removed from the site of damage.

**Mechanism of inflammation**

In and around the inflamed tissue there is an accumulation of edema fluid the endothelial wall of peripheral vascular bed. In initial stage the escape of fluid i.e., due to vasodilatation and consequent elevation in hydrostatic pressure, the characteristic inflammatory
oedema and exudates appear by increased vascular permeability of microcirculation.

Many drugs produced a dramatic symptomatic improvement in rheumatic processes. Non steroidal antiinflammatory drugs (NSAIDs) have analgesic, antipyretic and antiinflammatory effects. Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes, but all of them shared the common undesirable effect i.e, gastrointestinal irritation. The greatest risk from using antiinflammatory agents is that of gastrointestinal ulceration or bleeding. This can occur at any time in patients using these medications, with or without warning. Minor gastrointestinal problems such as dyspepsia are common with these agents. Nonsteroidal antiinflammatory agents can have adverse effects on the kidneys. A rare side effect from nonsteroidal antiinflammatory medications is liver damage.

Some uncommon but possible side effects from nonsteroidal antiinflammatory medications also include headache, dizziness, drowsiness and light headedness, itching, sweating, ringing in the ears, visual disturbances, swelling of the extremities, shortness of breath, palpitations, or thirst.
1.3. STATINES

Statins is the nick name for HMG-CoA reductase inhibitors and well established for treating high cholesterol. Statin research started with Japanese researchers Endo and Kuroda in 1971 and within a decade Merck has launched lovastatin (Mevacor), the first statin drug. Today, statins are the second most common class of drugs prescribed in the US after analgesics, and are commonly used for hyperlipidemia and to reduce the risk of heart attack and stroke. What makes statins intriguing is that these drugs have other biological actions beyond the lowering of cholesterol which makes them potentially useful in a bewildering array of medical conditions such as autoimmune conditions, organ transplantation, polycystic ovarian syndrome (PCOS), arrhythmias, chronic obstructive pulmonary disease (COPD), sepsis, contrast induced nephropathy, cataract, age related macular degeneration, subarachnoid hemorrhage, osteoporosis, dementia, asthma, thromboembolism, alzheimer and even cancer. As a class, statins have diverse biological effects including improving endothelial function, stabilizing atherosclerotic plaques, attenuating oxidative stress and inflammation, immunomodulation, as well as inhibition the thrombogenic response. Many of these actions are executed via a modulation or inhibition of post translational protein prenylation (also called isoprenylation).

In addition to their cholesterol lowering effects, statins have been reported to display additional pharmacological properties such as
antiviral and antitumor activities, however the antitumor molecular mechanisms by which the statin block cancer cell growth are poorly understood, and there are emerging interests to explore the anticancer potentials of HMGCoA reductase inhibitors in the clinical setting, particularly in tumor sites sensitive to these agents in vitro, some mechanism proposes for anticancer activities are apoptotic inducer, antiangiogenic and antimetastatic. These properties are associates with the inhibition of the synthesis of isoprenoid intermediates of the mevalonate pathway. Although several methods have been developed for statin quantification, their pharmacological properties have been disregarded and there is no cytotoxic evaluation in tumoral cell lines for some synthetic statins such as rosuvastatin and fluvastatin, since only exists study for the natural statins such as mevastatin and lovastatin.

Statins have been shown to inhibit proliferation and to induce apoptosis in a variety of tumor cells. They have also been found to display antitumor effects against melanoma, mammary carcinoma, pancreatic adenocarcinoma, fibrosarcoma, glioma, neuroblastoma, and lymphoma in animal tumor models resulting in retardation of tumor growth, and/or inhibition of the metastatic process. In pre clinical studies statins have also been demonstrated to potentiate the antitumor effects of some cytokines and chemotherapeutics. The molecular mechanisms underlying antitumor activity of statins have not been fully elucidated but interference with the function of Ras and Rho family
GTPases, inhibition of the activity of certain cyclin dependent kinases (CDK), and activation of CDK inhibitors, all seem to participate in this activity. Phase I trials of statins in humans have demonstrated myotoxicity as their main dose limiting toxicity, and phase II trials in various tumor types are ongoing to evaluate their efficacy. Future directions in the development of the statins as anticancer agents include combinations with chemotherapeutic or other molecular targeted agents, combinations with radiotherapy, maintenance therapy in minimal disease status, and as chemopreventive therapy.

A recent report demonstrated a direct antimicrobial effect of simvastatin and to a lesser extent fluvastatin against methicillin susceptible and methicillin resistant *Staphylococcus aureus* (MSSA and MRSA). Rosuvastatin exhibits high hydrophilicity and hepato selectivity, as well as low systemic bioavailability, while undergoing minimal metabolism via the cytochrome P450 system. Therefore, rosuvastatin has an interesting pharmacokinetic profile that is different from that of other statins. However, it remains to be established whether this may translate into a better safety profile and fewer drug-drug interactions for this statin compared with others. As with other statins, rosuvastatin treatment is associated with relatively low rates of severe myopathy, rhabdomyolysis, and renal failure. Asymptomatic liver enzyme elevations occur with rosuvastatin at a similarly low incidence as with other statins. Rosuvastatin treatment has also been associated with adverse effects
related to the gastrointestinal tract and central nervous system, which are also commonly observed with many other drugs. Proteinuria induced by rosuvastatin is likely to be associated with a statin provoked inhibition of low molecular weight protein reabsorption by the renal tubules. Higher doses of rosuvastatin have been associated with cases of renal failure. Also, the coadministration of rosuvastatin with drugs that increase rosuvastatin blood levels may be deleterious for the kidney. Furthermore, rhabdomyolysis, considered a class effect of statins, is known to involve renal damage. Concerns have been raised by findings from the Jupiter study suggesting that rosuvastatin may slightly increase the incidence of physician reported diabetes mellitus, as well as the levels of glycated hemoglobin in older patients with multiple risk factors and low grade inflammation. Drugs that antagonize organic anion transporter protein 1B1-mediated hepatic uptake of rosuvastatin are more likely to interact with this statin.

On the other hand, rosuvastatin combination treatment with fenofibrate, ezetimibe, omega-3-fatty acids, antifungal azoles, rifampin (rifampicin), or clopidogrel seems to be safe, as there is no evidence to support any pharmacokinetic or pharmacodynamic interaction of rosuvastatin with any of these drugs. Rosuvastatin therefore appears to be relatively safe and well tolerated, sharing the adverse effects that are considered class effects of statins. If the apparent antimicrobial activity represents a class effect, it was hypothesised that two other commonly
used statins, atorvastatin and rosuvastatin, may also have antimicrobial action *in vitro* against a variety of both Gram positive and Gram negative organisms. The study demonstrates that statins have a reproducible bacteriostatic effect *in vitro*. Rosuvastatin (marketed by AstraZeneca as Crestor) is a member of the drug class of statins, used to treat high cholesterol and related conditions, and to prevent cardiovascular disease. It was reported that the antimicrobial action of rosuvastatin required high concentrations\(^{15}\) (>800 mg/l) to achieve a reliable antimicrobial effect.

Recent clinico epidemiologic studies correlate patients receiving statin therapy with reduced mortality associated with severe bacterial infection\(^{16}\). Investigating the effect of statins on the innate immune capacity of phagocytic cells against the human pathogen *staphylococcus aureus*, uncovered a beneficial effect of statins on bacterial clearance by phagocytes, although, paradoxically, both phagocytosis and oxidative burst were inhibited. Probing instead for an extracellular mechanism of killing, it was found that statins boosted the production of antibacterial DNA based extracellular traps by human and murine neutrophils and also monocytes/macrophages. The effect of statins to induce phagocyte ETs was linked to sterol pathway inhibition.

Atorvastatin was reported\(^{17,18}\) as a potential antimalarial drug in *in vitro* combinational therapy with dihydroartemisinin, atorvastatin was shown synergistic effect.
1.4. REFERENCES


